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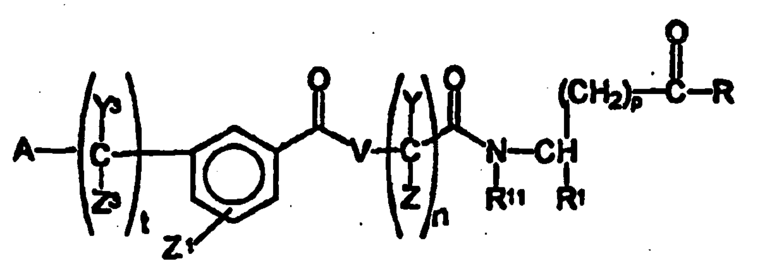
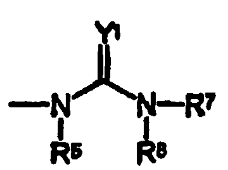
(57) Abstract

The present invention relates to a class of compounds represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein A is (a) or (b) or (c) or (d) pharmaceutical compositions thereof and methods of using such compounds and compositions as $\alpha_v\beta_3$ integrin antagonists.



(I)



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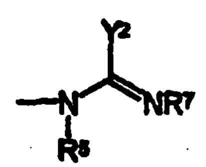

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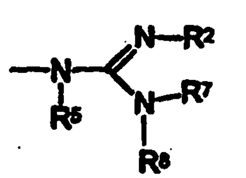

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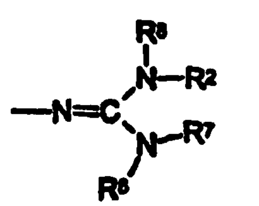

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META-GUANIDINE, UREA, THIOUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

The present application claims priority under 35 USC §119(e) of United States provisional application Serial No. 60/003,277 filed August 30, 1995.

Field of the Invention

The present invention relates to pharmaceutical agents (compounds) which are useful as $\alpha_v\beta_3$ integrin antagonists and as such are useful in pharmaceutical compositions and in methods for treating conditions mediated by $\alpha_v\beta_3$ by inhibiting or antagonizing $\alpha_v\beta_3$ integrins.

Background of the Invention

Integrins are a group of cell surface glycoproteins which mediate cell adhesion and therefore are useful mediators of cell adhesion interactions which occur during various biological processes. Integrins are heterodimers composed of noncovalently linked α and β polypeptide subunits. Currently eleven different α subunits have been identified and six different β subunits have been identified. The various α subunits can combine with various β subunits to form distinct integrins.

The integrin identified as $\alpha_v\beta_3$ (also known as the vitronectin receptor) has been identified as an integrin which plays a role in various conditions or disease states including tumor metastasis, solid tumor growth (neoplasia), osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, angiogenesis, including tumor angiogenesis, retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis and smooth muscle cell migration (e.g. restenosis). Additionally, it has been found that such agents would be useful as antivirals, antifungals and antimicrobials. Thus, compounds which sel ctively

inhibit or antagonize $\alpha_v\beta_3$ would be beneficial for treating such conditions.

It has been sh wn that the $\alpha_v\beta_3$ integrin and other α_v containing integrins bind to a number of Arg-Gly-Asp (RGD) containing matrix macromolecules. Compounds containing the RGD sequence mimic extracellular matrix ligands so as to bind to cell surface receptors. However, it is also known that RGD peptides in general are non-selective for RGD dependent integrins. For example, most RGD peptides which bind to $\alpha_v\beta_3$ also bind to $\alpha_v\beta_5$, $\alpha_v\beta_1$ and $\alpha_{IIb}\beta_3$. Antagonism of platelet $\alpha_{IIb}\beta_3$ (also known as the fibrinogen receptor) is known to block platelet aggregation in humans. In order to avoid bleeding side-effects when treating the conditions or disease states associated with the integrin $\alpha_v\beta_3$, it would be beneficial to develop compounds which are selective antagonists of $\alpha_v\beta_3$ as opposed to $\alpha_{IIb}\beta_3$.

Tumor cell invasion occurs by a three step process: 1) tumor cell attachment to extracellular matrix; 2) proteolytic dissolution of the matrix; and 3) movement of the cells through the dissolved barrier. This process can occur repeatedly and can result in metastases at sites distant from the original tumor.

Seftor et al. (Proc. Natl. Acad. Sci. USA, Vol. 89 (1992) 1557-1561) have shown that the $\alpha_v\beta_3$ integrin has a biological function in melanoma cell invasion. Montgomery et al., (Proc. Natl. Acad. Sci. USA, Vol. 91 (1994) 8856-60) have demonstrated that the integrin $\alpha_v\beta_3$ expressed on human melanoma cells promotes a survival signal, protecting the cells from apoptosis. Mediation of the tumor cell metastatic pathway by interference with the $\alpha_v\beta_3$ integrin cell adhesion receptor to impede tumor metastasis would be beneficial.

Brooks et al. (Cell, Vol. 79 (1994) 1157-1164) have demonstrated that antagonists of $\alpha_v\beta_3$ provide a therapeutic approach for the treatment of neoplasia (inhibition of s lid tumor growth) since systemic

administration of $\alpha_v\beta_3$ antagonists causes dramatic regression of various histologically distinct human tumors.

The adhesion receptor integrin $\alpha_v\beta_3$ was identified as a marker of angiogenic blood vessels in chick and man and therefore such receptor plays a critical role in angiogenesis or neovascularization. Angiogenesis is characterized by the invasion, migration and proliferation of smooth muscle and endothelial cells. Antagonists of $\alpha_v\beta_3$ inhibit this process by selectively promoting apoptosis of cells in neovasculature. The growth of new blood vessels, or angiogenesis, also contributes to pathological conditions such as diabetic retinopathy (Adonis et al., Amer. J. Ophthal., Vol. 118, (1994) 445-450) and rheumatoid arthritis (Peacock et al., J. Exp. Med., Vol. 175, (1992), 1135-1138). Therefore, $\alpha_v\beta_3$ antagonists would be useful therapeutic targets for treating such conditions associated with neovascularization (Brooks et al., Science, Vol. 264, (1994), 569-571).

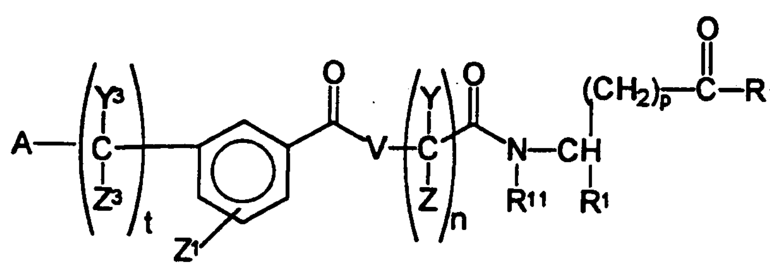
It has been reported that the cell surface receptor $\alpha_v\beta_3$ is the major integrin on osteoclasts responsible for attachment to bone. Osteoclasts cause bone resorption and when such bone resorbing activity exceeds bone forming activity it results in osteoporosis (a loss of bone), which leads to an increased number of bone fractures, incapacitation and increased mortality. Antagonists of $\alpha_v\beta_3$ have been shown to be potent inhibitors of osteoclastic activity both *in vitro* [Sato et al., J. Cell. Biol., Vol. 111 (1990) 1713-1723] and *in vivo* [Fisher et al., Endocrinology, Vol. 132 (1993) 1411-1413]. Antagonism of $\alpha_v\beta_3$ leads to decreased bone resorption and therefore restores a normal balance of bone forming and resorbing activity. Thus it would be beneficial to provide antagonists of osteoclast $\alpha_v\beta_3$ which are ffective inhibitors of bone r sorption and ther fore are useful in th treatment or prevention of osteoporosis.

The role of the $\alpha_v\beta_3$ int grin in smooth muscle cell migration also makes it a therapeutic target for prevention or inhibition of neointimal hyperplasia which is a leading cause of restenosis after vascular procedures (Choi et al., J. Vasc. Surg. Vol. 19(1) (1994) 125-34). Prevention or inhibition of neointimal hyperplasia by pharmaceutical agents to prevent or inhibit restenosis would be beneficial.

White (Current Biology, Vol. 3(9)(1993) 596-599) has reported that adenovirus uses $\alpha_v\beta_3$ for entering host cells. The integrin appears to be required for endocytosis of the virus particle and may be required for penetration of the viral genome into the host cell cytoplasm. Thus compounds which inhibit $\alpha_v\beta_3$ would find usefulness as antiviral agents.

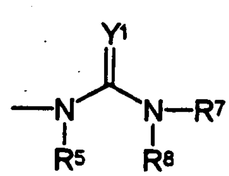
Summary of the Invention

The present invention relates to a class of compounds represented by the Formula I



or a pharmaceutically acceptable salt thereof, wherein

A is



wherein Y^1 is selected from the group consisting of N-R^2, O, and S;

R^2 is selected from the group consisting of H; alkyl; aryl; hydroxy; alkoxy; cyano; nitro; amino; alkenyl; alkynyl; amido; alkylcarbonyl; arylcarbonyl; alkoxycarbonyl; aryloxycarbonyl; haloalkylcarbonyl; haloalkoxycarbonyl; alkylthiocarbonyl; arylthiocarbonyl; acyloxymethoxycarbonyl; alkyl optionally substituted with one or more substituent selected from lower alkyl, halogen, hydroxyl, haloalkyl, cyano, nitro, carboxyl, amino, alkoxy, aryl or aryl optionally substituted with one or more halogen, haloalkyl, lower alkyl, alkoxy, cyano, alkylsulfonyl, alkylthio, nitro, carboxyl, amino, hydroxyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, or fused monocyclic heterocycles; aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, hydroxy, lower alkyl, alkoxy, methylenedioxy, ethylenedioxy, cyano, nitro, alkylthio, alkylsulfonyl, sulfonic acid, sulfonamide, carboxyl derivatives, amino, aryl, fused aryl, monocyclic heterocycles and fused monocyclic heterocycle; monocyclic heterocycles; and monocyclic heterocycles optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, amino, nitro, hydroxy, carboxyl derivatives, cyano, alkylthio, alkylsulfonyl, sulfonic acid, sulfonamide, aryl or fused aryl; or

R^2 taken together with R^7 forms a 4-12 membered dinitrogen containing heterocycle optionally substituted with one or more substituent selected from the group consisting of lower alkyl, hydroxy,

keto, alkoxy, halo, phenyl, amino, carboxyl or carboxyl ester, and fused phenyl;

or R^2 taken together with R^7 forms a 5 membered heteroaromatic ring optionally substituted with one or more substituent selected from lower alkyl, phenyl and hydroxy;

or R^2 taken together with R^7 forms a 5 membered heteroaromatic ring fused with a phenyl group;

R^7 (when not taken together with R^2) and R^8 are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; aralkyl; amino; alkylamino; hydroxy; alkoxy; arylamino; amido, alkylcarbonyl, arylcarbonyl; alkoxycarbonyl; aryloxy; aryloxycarbonyl; haloalkylcarbonyl; haloalkoxycarbonyl; alkylthiocarbonyl; arylthiocarbonyl; acyloxymethoxycarbonyl; cycloalkyl; bicycloalkyl; aryl; acyl; benzoyl; alkyl optionally substituted with one or more substituent selected from lower alkyl, halogen, hydroxy, haloalkyl, cyano, nitro, carboxyl derivatives, amino, alkoxy, thio, alkylthio, sulfonyl, aryl, aralkyl, aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitro, carboxyl derivatives, aryloxy, amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethyl, sulfonyl, alkylsulfonyl, haloalkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, fused m nocyclic heterocycles; aryl optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alk xy,

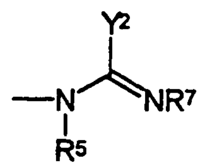
methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitr , carboxyl derivatives, aryloxy, amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethylsulfonyl, alkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles, or fused monocyclic heterocycles; monocyclic heterocycles; monocyclic heterocycles optionally substituted with one or more substituent selected from halogen, haloalkyl, lower alkyl, alkoxy, aryloxy, amino, nitro, hydroxy, carboxyl derivatives, cyano, alkylthio, alkylsulfonyl, aryl, fused aryl; monocyclic and bicyclic heterocyclicalkyls; $-SO_2R^{10}$ wherein R^{10} is selected from the group consisting of alkyl, aryl and monocyclic heterocycles, all optionally substituted with one or more substituent selected from the group consisting of halogen, haloalkyl, alkyl, alkoxy, cyano, nitro, amino, acylamino, trifluoroalkyl, amido, alkylaminosulfonyl, alkylsulfonyl, alkylsulfonylamino, alkylamino, dialkylamino, trifluoromethylthio, trifluoroalkoxy, trifluoromethylsulfonyl, aryl, aryloxy, thio, alkylthio, and monocyclic heterocycles; and

$-\overset{\displaystyle O}{\overset{\|}{C}}-R^{10}$ wherein R^{10} is defined above;

or NR^7 and R^8 taken together form a 4-12 membered mononitrogen containing monocyclic or bicyclic ring optionally substituted with one or more substituent selected from lower alkyl, carboxyl derivatives, aryl or hydroxy and wherein said ring ptionally contains a heteroatom selected from the group consisting of O, N and S;

R^5 is sel ct d from the group consisting f H, alkyl, alkenyl, alkynyl, benzyl, and phenethyl;

or

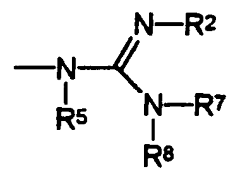
A is 

wherein Y^2 is selected from the group consisting of alkyl; cycloalkyl; bicycloalkyl; aryl; monocyclic heterocycles; alkyl optionally substituted with aryl which can also be optionally substituted with one or more substituent selected from halo, haloalkyl, alkyl, nitro, hydroxy, alkoxy, aryloxy, aryl, or fused aryl; aryl optionally substituted with one or more substituent selected from halo, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, fused aryl, nitro, methylenedioxy, ethylenedioxy, or alkyl; alkynyl; alkenyl; -S-R^9 and -O-R^9 wherein R^9 is selected from the group consisting of H; alkyl; aralkyl; aryl; alkenyl; and alkynyl; or R^9 taken together with R^7 forms a 4-12 membered mononitrogen and monosulfur or monooxygen containing heterocyclic ring optionally substituted with lower alkyl, hydroxy, keto, phenyl, carboxyl or carboxyl ester, and fused phenyl; or R^9 taken together with R^7 is thiazole; oxazole; benzoxazole; or benzothiazole; and

R^5 and R^7 are as defined above;

or Y^2 (when Y^2 is carbon) taken together with R^7 forms a 4-12 membered mononitrogen or dinitrogen containing ring optionally substituted with alkyl, aryl, keto or hydroxy;

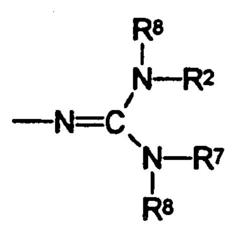
or A is



where R^2 and R^7 taken together form a 5-8 membered dinitrogen containing heterocycle optionally substituted with one or more substituent selected from the group consisting of lower alkyl, hydroxy, keto, phenyl, or carboxyl derivatives; and R^8 is selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylthiocarbonyl, or acyloxymethoxycarbonyl; and

R^5 is defined as above

or A is



where R^2 and R^7 taken together form a 5-8 membered dinitrogen containing heterocycle optionally substituted with hydroxy, keto, phenyl, or alkyl; and

R^8 are both selected from the group consisting of alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylthiocarbonyl and acyloxymeth xycarbonyl;

Z^1 is one or more substituent selected from the gr up consisting of H; alkyl; hydroxy; alkoxy; aryloxy; halogen; haloalkyl; haloalkoxy; nitr ; amino; alkylamino; acylamino; dialkylamino; cyano; alkylthio; alkylsulfonyl; carboxyl derivatives; trihaloacetamide; acetamide; aryl; fused aryl; cycloalkyl; thio; monocyclic heterocycles; fused monocyclic heterocycles; and A, wherein A is defined above;

V is selected from the group consisting of $-N-(R^6)-$ wherein R^6 is selected from the group consisting of H; lower alkyl; cycloalkyl; aralkyl; aryl; and monocyclic heterocycles; or R^6 taken together with Y, forms a 4-12 membered mononitrogen containing ring;

Y, Y^3, Z and Z^3 are independently selected from the group consisting of hydrogen; alkyl; aryl; and cycloalkyl; or Y and Z taken together form a cycloalkyl; or Y^3 and Z^3 taken together form a cycloalkyl;

n is an integer 1, 2, or 3;

t is an integer 0, 1, or 2;

p is an integer 0, 1, 2, or 3;

R is $X-R^3$ wherein X is selected from the group consisting of O, S and NR^4, wherein R^3 and R^4 are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; haloalkyl; aryl; arylalkyl; sugars; steroids; polyalkylethers; alkylamido; alkyl N,N-dialkylamido; pivaloyloxymethyl; and in the case

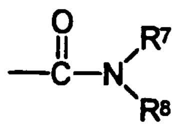
of th free acid, all pharmaceutically acceptable salts th reof;

R^1 is selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; carboxyl derivatives; haloalkyl; cycloalkyl; monocyclic heterocycles; monocyclic heterocycles optionally substituted with alkyl, halogen, haloalkyl, cyano, hydroxy, aryl, fused aryl, nitro, alkoxy, aryloxy, alkylsulfonyl, arylsulfonyl, sulfonamide, thio, alkylthio, carboxyl derivatives, amino, amido;

alkyl optionally substituted with one or more of halo, haloalkyl, hydroxy, alkoxy, aryloxy, thio, alkylthio, alkynyl, alkenyl, alkyl, arylthio, alkylsulfoxide, alkylsulfonyl, arylsulfoxide, arylsulfonyl, cyano, nitro, amino, alkylamino, dialkylamino, alkylsulfonamide, arylsulfonamide, acylamide, carboxyl derivatives, sulfonamide, sulfonic acid, phosphonic acid derivatives, phosphinic acid derivatives, aryl, arylthio, arylsulfoxide, or arylsulfone all optionally substituted on the aryl ring with halo, alkyl, haloalkyl, cyano, nitro, hydroxy, carboxyl derivatives, alkoxy, aryloxy, amino, alkylamino, dialkylamino, amido, aryl, fused aryl, monocyclic heterocycles; and fused monocyclic heterocycles, monocyclic heterocyclicthio, monocyclic heterocyclicsulfoxide, and monocyclic heterocyclic sulfone, which can be optionally substituted with halo, haloalkyl, nitro, hydroxy, alkoxy, fused aryl, or alkyl;

alkylcarbonyl, haloalkylcarbonyl, and arylcarbonyl;

aryl optionally substituted in one or more positions with halo, haloalkyl, alkyl, alkoxy, aryl xy, methylenedioxy, ethylenedioxy, alkylthio, haloalkylthio, thio, hydroxy, cyano, nitro, acyloxy, carboxyl derivatives, carboxyalkoxy; amido, acylamino, amino, alkylamino, dialkylamino, trifluoroalkoxy, trifluoromethylsulfonyl, alkylsulfonyl, sulfonic acid, sulfonamide, aryl, fused aryl, monocyclic heterocycles and fused monocyclic heterocycles; and

 wherein R^7 and R^8 are as defined above

and provided that taken together with the nitrogen, R^7 and R^8 comprise an amino acid;

and

R^{11} is selected from the group consisting of H, alkyl, aralkyl, alkenyl, alkynyl, haloalkyl or haloalkynyl or R^{11} taken together with Y forms a 4-12 membered mononitrogen containing ring.

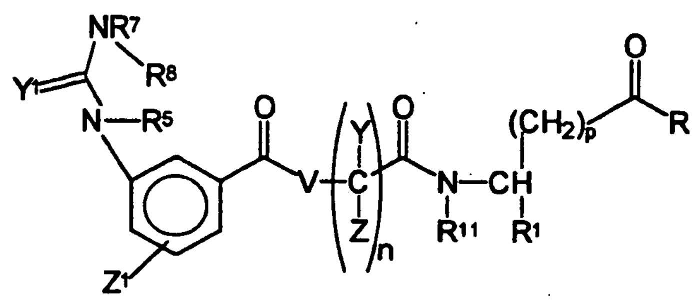
It is another object of the invention to provide pharmaceutical compositions comprising compounds of the Formula I. Such compounds and compositions are useful in selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin and therefore in another embodiment the present invention relates to a method of selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin. The invention further involves treating or inhibiting pathological conditions associated therewith such as osteoporosis, humoral hypercalcemia of malignancy, Pag t's disease, tumor metastasis, solid tumor growth (neoplasia), angiogenesis, including tumor

angiogenesis, retinopathy including diabetic retinopathy, arthritis, including rh umatoid arthritis, periodontal disease, psoriasis, smooth muscle cell migration and restenosis in a mammal in need of such treatment. Additionally, such pharmaceutical agents are useful as antiviral agents, and antimicrobials.

Detailed Description

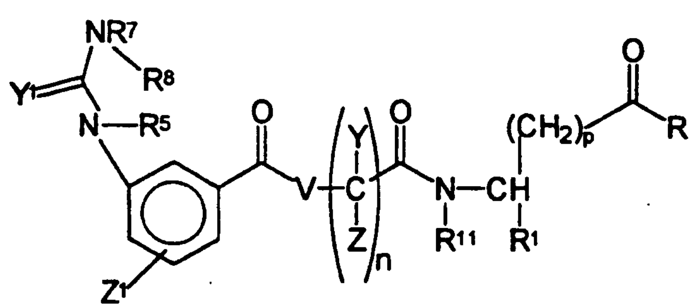
The present invention relates to a class of compounds represented by the Formula I, described above.

A preferred embodiment of the present invention is a compound of the Formula II



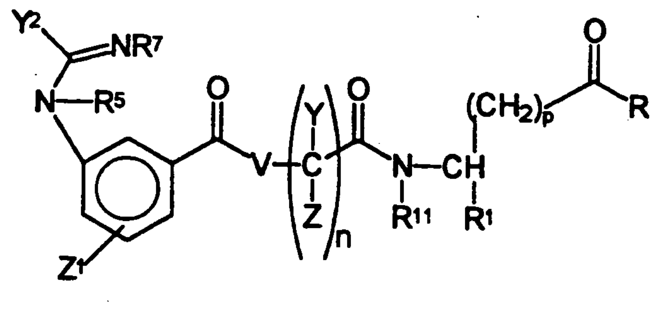
wherein R^5, R^7 and R^8 are independently selected from H, alkyl, aryl, carboxyalkyl, substituted aryl, substituted arylsulfonyl, and arylalkyl or NR^7 and R^8 taken together form a 4-12 membered mononitrogen containing ring optionally substituted and the other variables are as described in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula III



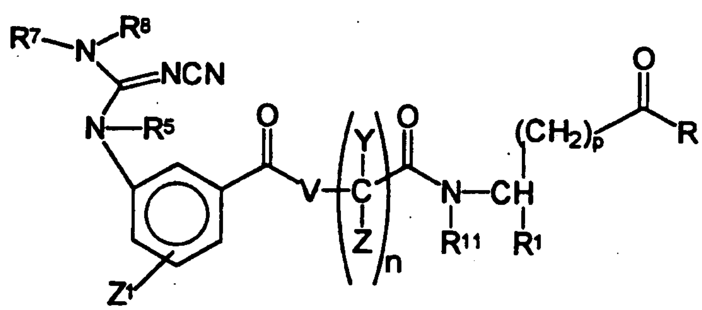
wherein Y^1 is $-NR^2$ and R^2 taken together with R^7 forms an optionally substituted 4-12 membered ring and the other variables are as defined above in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula IV



wherein Y^2 taken together with R^7 forms a 4-12 membered ring and the other variables are as defined above in Formula I.

Another preferred embodiment of the present invention is a compound of the Formula V



wherein the variables are as defined above in Formula I.

The invention further relates to pharmaceutical compositions containing therapeutically effective amounts of the compounds of Formulas I-V.

The invention also relates to a method of selectively inhibiting or antagonizing the $\alpha_v\beta_3$ integrin and more specifically relates to a method of inhibiting bone resorption, periodontal disease, osteoporosis, humoral hypercalcemia of malignancy, Paget's dis as , tum r metastasis, solid tumor gr wth (neoplasia),

angiogenesis, including tumor angiog nesis, retinopathy including diabetic retinopathy, arthritis, including rheumatoid arthritis, smooth muscle cell migration and restenosis by administering a therapeutically effective amount of a compound of the Formula I-V to achieve such inhibition together with a pharmaceutically acceptable carrier.

The following is a list of definitions of various terms used herein:

As used herein, the terms "alkyl" or "lower alkyl" refer to a straight chain or branched chain hydrocarbon radicals having from about 1 to about 10 carbon atoms, and more preferably 1 to about 6 carbon atoms. Examples of such alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, hexyl, isohexyl, and the like.

As used herein the terms "alkenyl" or "lower alkenyl" refer to unsaturated acyclic hydrocarbon radicals containing at least one double bond and 2 to about 6 carbon atoms, which carbon-carbon double bond may have either <u>cis</u> or <u>trans</u> geometry within the alkenyl moiety, relative to groups substituted on the double bond carbons. Examples of such groups are ethenyl, propenyl, butenyl, isobutenyl, pentenyl, hexenyl and the like.

As used herein the terms "alkynyl" or "lower alkynyl" refer to acyclic hydrocarbon radicals containing one or more triple bonds and 2 to about 6 carbon atoms. Examples of such groups are ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

The term "cycloalkyl" as used herein means saturated or partially unsaturated cyclic carbon radicals containing 3 to about 8 carbon atoms and more preferably 4 to about 6 carbon atoms. Examples f such cycloalkyl radicals include cyclopropyl, cyclopropenyl,

cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, and the like.

The term "aryl" as used herein denotes aromatic ring systems composed of one or more aromatic rings. Preferred aryl groups are those consisting of one, two or three aromatic rings. The term embraces aromatic radicals such as phenyl, pyridyl, naphthyl, thiophene, furan, biphenyl and the like.

As used herein, the term "cyano" is represented by a radical of the formula $\wr\!\!-CN$.

The terms "hydroxy" and "hydroxyl" as used herein are synonymous and are represented by a radical of the formula $\wr\!\!-OH$.

The term "lower alkylene" or "alkylene" as used herein refers to divalent linear or branched saturated hydrocarbon radicals of 1 to about 6 carbon atoms.

As used herein the term "alkoxy" refers to straight or branched chain oxy containing radicals of the formula $-OR^{20}$, wherein R^{20} is an alkyl group as defined above. Examples of alkoxy groups encompassed include methoxy, ethoxy, n-propoxy, n-butoxy, isopropoxy, isobutoxy, sec-butoxy, t-butoxy and the like.

As used herein the terms "arylalkyl" or "aralkyl" refer to a radical of the formula $\wr\!\!-R^{22}-R^{21}$ wherein R^{21} is aryl as defined above and R^{22} is an alkylene as defined above. Examples of aralkyl groups include benzyl, pyridylmethyl, naphthylpropyl, phenethyl and the like.

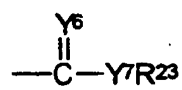
As used herein the term "nitro" is represented by a radical of the formula $\wr\!\!-NO_2$.

As used herein the term "halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

As used herein the term "haloalkyl" refers to alkyl groups as defined above substituted with one or more of the same or different halo groups at one or more carbon atom. Examples of haloalkyl groups include trifluoromethyl, dichloroethyl, fluoropropyl and the like.

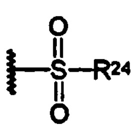
As used herein the term "carboxyl" or "carboxy" refers to a radical of the formula -COOH.

As used herein the term "carboxyl ester" refers to a radical of the formula $-COOR^{23}$ wherein R^{23} is selected from the group consisting of H, alkyl, aralkyl or aryl as defined above.

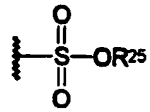
As used herein the term "carboxyl derivative" refers to a radical of the formula  wherein Y^6 and Y^7 are independently selected from the group consisting of O, N or S and R^{23} is selected from the group consisting of H, alkyl, aralkyl or aryl as defined above.

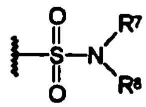
As used herein the term "amino" is represented by a radical of the formula $-NH_2$.

As used herein the term "alkylsulfonyl" or "alkylsulfone" refers to a radical of the formula

 wherein R^{24} is alkyl as defined above.

As used herein the term "alkylthio" refers to a radical of the formula $-SR^{24}$ wherein R^{24} is alkyl as defined above.

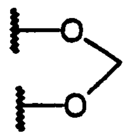
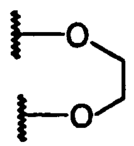
As used herein the term "sulfonic acid" refers to a radical of th formula  wherein R^{25} is H, alkyl or aryl as defined above.

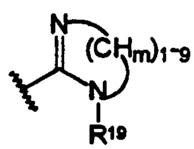
As used herein the term "sulfonamide" refers to a radical of the formula  wherein R^7 and R^8 are as defined above.

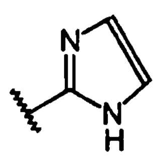
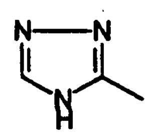
As used herein the term "fused aryl" refers to an aromatic ring such as the aryl groups defined above fused to one or more phenyl rings. Embraced by the term "fused aryl" is the radical naphthyl.

As used herein the terms "monocyclic heterocycle" or "monocyclic heterocyclic" refer to a monocyclic ring containing from 4 to about 12 atoms, and more preferably from 5 to about 10 atoms, wherein 1 to 3 of the atoms are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur with the understanding that if two or more different heteroatoms are present at least one of the heteroatoms must be nitrogen. Representative of such monocyclic heterocycles are imidazole, furan, pyridine, oxazole, pyran, triazole, thiophene, pyrazole, thiazole, thiadiazole, and the like.

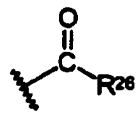
As used herein the term "fused monocyclic heterocycle" refers to a monocyclic heterocycle as defined above with a benzene fused thereto. Examples of such fused monocyclic heterocycles include benzofuran, benzopyran, benzodioxole, benzothiazole, benzothiophene, benzimidazole and the like.

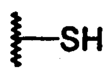
As used herein the term "methylenedioxy" refers to the radical  and the term "ethylenedioxy" refers to the radical .

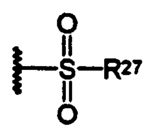
As used herein the term "4-12 membered dinitrogen containing heterocycle refers to a radical of the formula  wherein m is 1 or 2 and R^{19} is H, alkyl, aryl, or aralkyl and more preferably refers to 4-9 membered ring and includes rings such as imidazoline.

As used herein the term "5-membered optionally substituted heteroaromatic ring" includes for example a radical of the formula  or  and "5-membered heteroaromatic ring fused with a phenyl" refers to such a "5-membered heteroaromatic ring" with a phenyl fused thereto. Representative of such 5-m mbered heteroaromatic rings fused with a phenyl is benzimidazole.

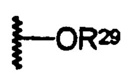
As used herein the term "bicycloalkyl" refers t a bicyclic hydrocarbon radical c ntaining 6 to ab ut 12 carbon atoms which is saturated or partially unsaturated.

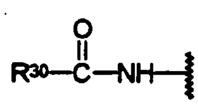
As used herein the term "acyl" refers to a radical of the formula  wherein R^{26} is alkyl, alkenyl, alkynyl, aryl or aralkyl and optionally substituted thereon as defined above. Encompassed by such radical are the groups acetyl, benzoyl and the like.

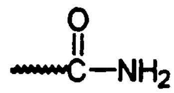
As used herein the term "thio" refers to a radical of the formula  .

As used herein the term "sulfonyl" refers to a radical of the formula  wherein R^{27} is alkyl, aryl or aralkyl as defined above.

As used herein the term "haloalkylthio" refers to a radical of the formula $-S-R^{28}$ wherein R^{28} is haloalkyl as defined above.

As used herein the term "aryloxy" refers to a radical of the formula  wherein R^{29} is aryl as defined above.

As used herein the term "acylamino" refers to a radical of the formula  wherein R^{30} is alkyl, aralkyl or aryl as defined abov .

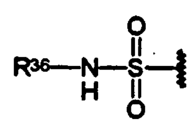
As used herein the term "amido" refers to a radical of the formula  .

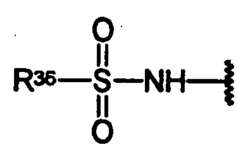
As used herein the term "alkylamino" refers to a radical of the formula $-NHR^{32}$ wherein R^{32} is alkyl as defined above.

As used herein the term "dialkylamino" refers to a radical of the formula $-NR^{33}R^{34}$ wherein R^{33} and R^{34} are the same or different alkyl groups as defined above.

As used herein the term "trifluoromethyl" refers to a radical of the formula $\text{—}CF_3$.

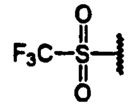
As used herein the term "trifluoroalkoxy" refers to a radical of the formula $F_3C\text{—}R^{35}\text{—}O\text{—}$ wherein R^{35} is a bond or an alkylene as defined above.

As used herein the term "alkylaminosulfonyl" refers to a radical of the formula  wherein R^{36} is alkyl as defined above.

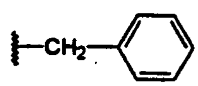
As used herein the term "alkylsulfonylamino" refers to a radical of the formula 

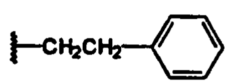
wherein R^{36} is alkyl as defined above.

As used herein the term "trifluoromethylthio" refers to a radical of the formula $F_3C\text{—}S\text{—}$.

As used her in th term "trifluoromethylsulfonyl" refers to a radical of the formula  .

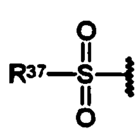
As used herein the term "4-12 membered mono-nitrogen containing monocyclic or bicyclic ring" refers to a saturated or partially unsaturated monocyclic or bicyclic ring of 4-12 atoms and more preferably a ring of 4-9 atoms wherein one atom is nitrogen. Such rings may optionally contain additional heteroatoms selected from nitrogen, oxygen or sulfur. Included within this group are morpholine, piperidine, piperazine, thiomorpholine, pyrrolidine, proline, azacycloheptene and the like.

As used herein the term "benzyl" refers to the radical  .

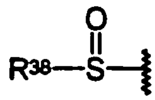
As used herein the term "phenethyl" refers to the radical  .

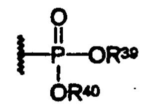
As used herein the term "4-12 membered mono-nitrogen containing monosulfur or monooxygen containing heterocyclic ring" refers to a ring consisting of 4 to 12 atoms and more preferably 4 to 9 atoms wherein at least one atom is a nitrogen and at least one atom is oxygen or sulfur. Encompassed within this definition are rings such as thiazoline and the like.

As used herein the term "arylsulfonyl" or "arylsulfone" refers to a radical of the formula

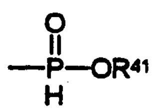
 wherein R^{37} is aryl as defined above.

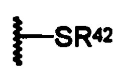
As used herein the terms "alkylsulfoxide" or "arylsulfoxide" refer to radicals of the formula

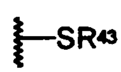
 wherein R^{38} is, respectively, alkyl or aryl as defined above.

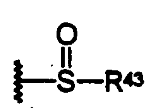
As used herein the term "phosphonic acid derivative" refers to a radical of the formula  wherein R^{39} and R^{40} are the same or different H, alkyl, aryl or aralkyl.

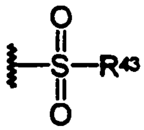
As used herein the term "phosphinic acid derivatives" refers to a radical of the formula

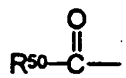
 wherein R^{41} is H, alkyl, aryl or aralkyl as defined above.

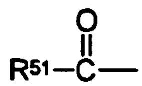
As used herein the term "arylthio" refers to a radical of the formula  wherein R^{42} is aryl as defined above.

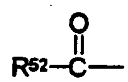
As used herein the term "monocyclic heterocycle thio" refers to a radical of the formula  wherein R^{43} is a monocyclic heterocycle radical as defined above.

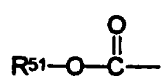
As used herein the terms "monocyclic heterocycle sulfoxide" and "monocyclic heterocycle sulfone" refer, respectively, to radicals of the formula  and

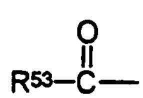
 wherein R^{43} is a monocyclic heterocycle radical as defined above.

As used herein the term "alkylcarbonyl" refers to a radical of the formula  wherein R^{50} is alkyl as defined above.

As used herein the term "arylcarbonyl" refers to a radical of the formula  wherein R^{51} is aryl as defined above.

As used herein the term "alkoxycarbonyl" refers to a radical of the formula  wherein R^{52} is alkoxy as defined above.

As used herein the term "aryloxycarbonyl" refers to a radical of the formula  wherein R^{51} is aryl as defined above.

As used herein the term "haloalkylcarbonyl" refers to a radical of the formula  wherein R^{53} is haloalkyl as defined above.

As used herein the term "haloalkoxycarbonyl" refers to a radical of the formula $R^{53}-O-\overset{\overset{\displaystyle O}{\|}}{C}-$ wherein R^{53} is haloalkyl as defined above.

As used herein the term "alkylthiocarbonyl" refers to a radical of the formula $R^{50}-S-\overset{\overset{\displaystyle O}{\|}}{C}-$ wherein R^{50} is alkyl as defined above.

As used herein the term "arylthiocarbonyl" refers to a radical of the formula $R^{51}-S-\overset{\overset{\displaystyle O}{\|}}{C}-$ wherein R^{51} is aryl as defined above.

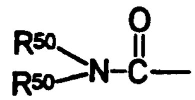
As used herein the term "acyloxymethoxycarbonyl" refers to a radical of the formula

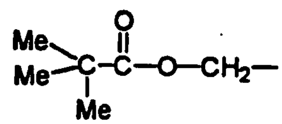
$R^{54}-O-CH_2-O-\overset{\overset{\displaystyle O}{\|}}{C}-$ wherein R^{54} is acyl as defined above.

As used herein the term "arylamino" refers to a radical of the formula R^{51}-NH- wherein R^{51} is aryl as defined above.

As used herein the term "polyalkylether" refers to commonly used glycols such as triethyleneglycol, tetraethylene glycol, polyethylene glycol and the like.

As used herein the term "alkylamido" refers to a radical of the formula $R^{50}-NH-\overset{\overset{\displaystyle O}{\|}}{C}-$ wherein R^{50} is alkyl as defined above.

As used herein the term "N,N-dialkylamido" refers t a radical of the formula  wherein R^{50} is the same or different alkyl group as defined above.

As used herein the term "pivaloyloxymethyl" refers to a radical of the formula .

As used herein the term "acyloxy" refers to a radical of the formula R^{55}-O- wherein R^{55} is acyl as defined above.

The term "composition" as used herein means a product which results from the mixing or combining of more than one element or ingredient.

The term "pharmaceutically acceptable carrier", as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician.

The following is a list of abbreviations and the corresponding meanings as used interchangeably herein:

^{1}H-NMR = proton nuclear magnetic resonance
AcOH = acetic acid
BH_3-THF = borane-tetrahydrofuran complex
Bn = benzyl
BOC = tert-butoxycarbonyl
ButLi = butyl lithium
Cat. = catalytic amount
CH_2Cl_2 = dichl romethane

CH_3CN = ac tonitrile
CH_3I = iodomethan
CHN analysis = carbon/hydrogen/nitrogen elemental analysis
CHNCl analysis = carbon/hydrogen/nitrogen/chlorine elemental analysis
CHNS analysis = carbon/hydrogen/nitrogen/sulfur elemental analysis
DCC = 1,3-dicyclohexylcarbodiimide
DIBAL = diisobutylaluminum hydride
DIEA = diisopropylethylamine
DMA = N,N-dimethylacetamide
DMAP = 4-(N,N-dimethylamino)pyridine
DMF = N,N-dimethylformamide
DSC = disuccinyl carbonate
EDCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et = ethyl
Et_2O = diethyl ether
Et_3N = triethylamine
EtOAc = ethyl acetate
EtOH = ethanol
FAB MS = fast atom bombardment mass spectroscopy
g = gram(s)
GIHA = *meta*-guanidinohippuric acid
GIHA HCl = meta-guanidinohippuric acid hydrochloride
HPLC = high performance liquid chromatography
IBCF = isobutylchloroformate
i-Pr = iso propyl
i-Prop = iso propyl
K_2CO_3 = potassium carbonate
KOH = potassium hydroxide
KSCN = potassium thiocyanate
LiOH = lithium hydroxide
MCPBA = m-chloroperoxybenzoic acid or m-chloroperbenzoic acid
Me = methyl
MeOH = methanol
MesCl = methanesulfonylchloride
mg = milligram
$MgSO_4$ = magnesium sulfate
ml = milliliter
mL = milliliter
MS = mass spectroscopy
N_2 = nitrogen
$NaCNBH_3$ = sodium cyanoborohydride
NaH - sodium hydride
$NaHCO_3$ = sodium bicarbonate
NaOH = sodium hydroxide
Na_2PO_4 = sodium phosphate
Na_2SO_4 = sodium sulfate
NEt_3 = triethylamine
NH_4HCO_3 = ammonium bicarbonate
$NH_4^+HCO_2^-$ = ammonium formate

NMM = N-methylmorpholine
NMR = nuclear magn tic resonance
RPHPLC = revers phase high performance liquid chromatography
RT = room temperature
Pd/C = palladium on carbon
Ph = phenyl
Pt/C = platinum on carbon
t-BOC = tert-butoxycarbonyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TMEDA = trimethylethylenediamine
TMS = trimethylsilyl
Δ = heating the reaction mixture

The compounds as shown in Formulas I-V can exist in various isomeric forms and all such isomeric forms are meant to be included. Tautomeric forms are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

In the structures and formulas herein, a bond drawn across a bond of a ring can be to any available atom on the ring.

The term "pharmaceutically acceptable salt" refers to a salt prepared by contacting a compound of Formula I with an acid whose anion is generally considered suitable for human consumption. Examples of pharmacologically acceptable salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate salts and the like. All of the pharmacologically acceptable salts may be prepared by conventional means. (See Berge et al., J Pharm. Sci., 66(1), 1-19 (1977) for additional examples of pharmaceutically acceptable salts.)

For the selective inhibition or antagonism of $\alpha_v\beta_3$ integrins, compounds of the present invention may be administered orally, parenterally, or by inhalation spray, or topically in unit dosage formulations containing conventional pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes, for exampl , subcutaneous,

intravenous, intramuscular, intrasternal, infusi n techniques or intraperitonally.

The compounds of the present invention ar administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds required to prevent or arrest the progress of or to treat the medical condition are readily ascertained by one of ordinary skill in the art using preclinical and clinical approaches familiar to the medicinal arts.

Accordingly, the present invention provides a method of treating conditions mediated by selectively inhibiting or antagonizing the $\alpha_v\beta_3$ cell surface receptor which method comprises administering a therapeutically effective amount of a compound selected from the class of compounds depicted in Formulas I-V, wherein one or more compounds of the Formulas I-V is administered in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients. More specifically, the present invention provides a method for inhibition of the $\alpha_v\beta_3$ cell surface receptor. Most preferably the present invention provides a method for inhibiting bone resorption, treating osteoporosis, inhibiting humoral hypercalcemia of malignancy, treating Paget's disease, inhibiting tumor metastasis, inhibiting neoplasia (solid tumor growth), inhibiting angiogenesis including tumor angiogenesis, treating diabetic retinopathy, inhibiting arthritis, psoriasis and periodontal disease, and inhibiting smooth muscle cell migration including restenosis.

Based upon standard laboratory experimental techniques and proc dures well known and appreciated by those skill d in the art, as well as comparisons with

comp unds of known usefulness, th compounds of Formula I can be used in the treatment of patients suffering from the above pathological conditions. One skilled in the art will recognize that selection of the most appropriate compound of the invention is within the ability of one with ordinary skill in the art and will depend on a variety of factors including assessment of results obtained in standard assay and animal models.

Treatment of a patient afflicted with one of the pathological conditions comprises administering to such a patient an amount of compound of the Formula I which is therapeutically effective in controlling the condition or in prolonging the survivability of the patient beyond that expected in the absence of such treatment. As used herein, the term "inhibition" of the condition refers to slowing, interrupting, arresting or stopping the condition and does not necessarily indicate a total elimination of the condition. It is believed that prolonging the survivability of a patient, beyond being a significant advantageous effect in and of itself, also indicates that the condition is beneficially controlled to some extent.

As stated previously, the compounds of the invention can be used in a variety of biological, prophylactic or therapeutic areas. It is contemplated that these compounds are useful in prevention or treatment of any disease state or condition wherein the $\alpha_v\beta_3$ integrin plays a role.

The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regim n may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram

f body weight per day are useful in the treatment of th above-indicat d conditions.

The active ingredient administered by inj ction is formulated as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose would typically be about 0.01 to 10 mg/kg body weight injected per day in multiple doses depending on the factors listed above.

For administration to a mammal in need of such treatment, the compounds in a therapeutically effective amount are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

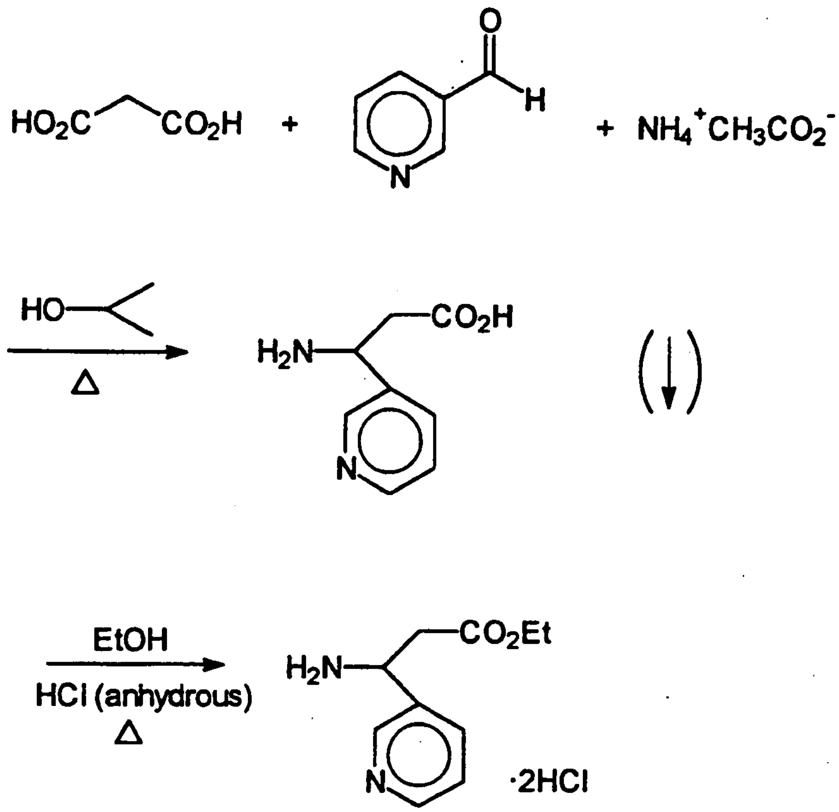
The pharmaceutical compositions useful in the present invention may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

The general synthetic sequences for preparing the compounds useful in the present invention are outlined in Schemes I-XXI. Both an explanation of, and the actual procedures for, th vari us aspects of the present invention are described where appropriate. The

following Schemes and Exampl s are intended t be merely illustrative f the present invention, and n t limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the Schemes and Examples can be used to synthesize the compounds of the present invention.

Unless otherwise indicated all starting materials and equipment employed were commercially available.

SCHEME I


HO2C
CO2H
+
O
H
N
+ NH4+CH3CO2-
HO
Δ
H2N
CO2H
N
(↓)
EtOH
HCl (anhydrous)
Δ
H2N
CO2Et
N
·2HCl

(A)

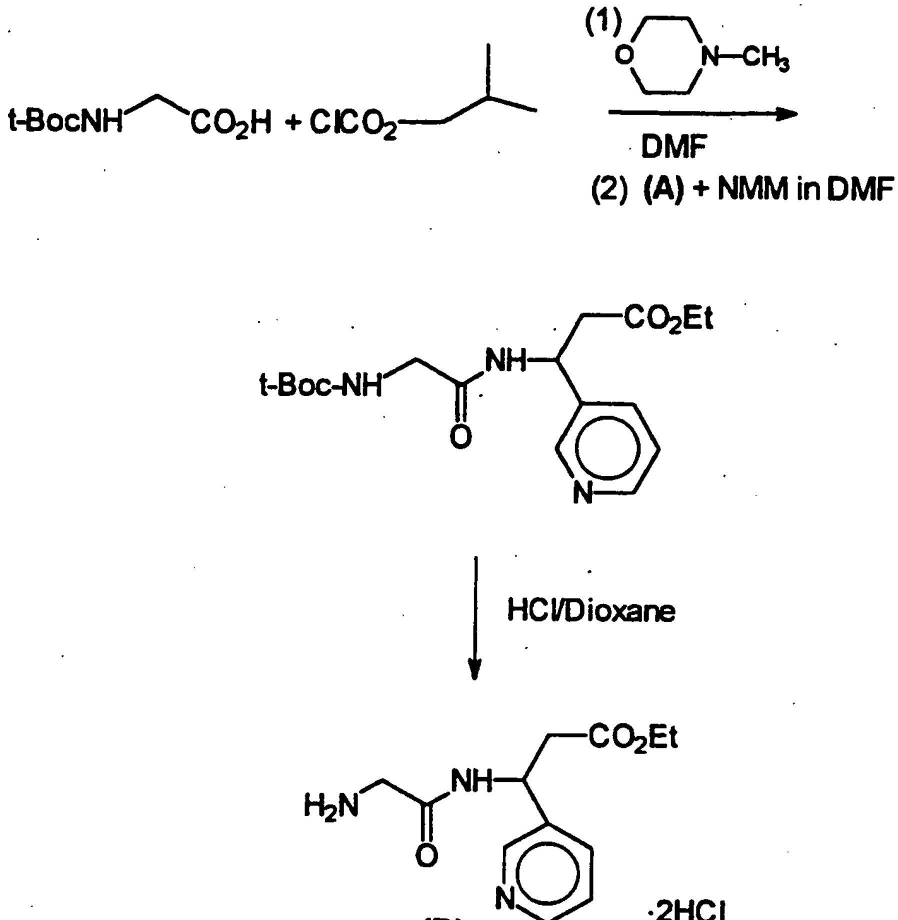
Scheme I describes a synthesis of a pyridyl β-amin acid which can be used to synth size compounds of the pr sent inv ntion wherein R^1 is pyridyl. The reaction can be modified using conventional methodology to prepare other aromatic, alkyl or heterocyclic substituted β-amino acids by substitution of the pyridyl carboxaldehyde with any other appropriate aldehyde. Briefly, in Scheme I to pyridine-carboxaldehyde in isopropanol is added ammonium acetate followed by malonic acid. The reaction mixture is stirred at reflux, the resulting precipitate filtered and washed with hot isopropanol and dried to yield 3-amino-3-(3-pyridyl)propionic acid. The ethyl ester is synthesized by heating this acid in excess ethanol in the presence of excess HCl gas.

Additionally, β-amino acids which are useful in the present invention are accessible through modified Knoevenagel reactions (Secor, H.V.; Edwards, W.B.J. J. Org. Chem. 1979, 44, 3136-40; Bellasoued, M.; Arous-Chtar, R.; Gaudemar, M.J.; J. Organometal. Chem. 1982, 231, 185-9), through Reformatski reaction with Schiff bases (Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. Chem. Pharm. Bull. 1978, 26, 260), Michael addition into an acrylic derivative (Davies, S.G.; Ichihara, O. Tetrahedron:Asymmetry 1991, 2, 183-6; Furukawa, M.; Okawara, TR.; Terawaki, Y. Chem. Pharm. Bull., 1977, 25, 1319-25). More recent methods include the use of organometallic reagents in Pd or Zn mediated couplings (Konopelski, J.; Chu, K.S.; Negrete, G.R. J. Org. Chem. 1991, 56, 1355; Mokhallalati, M.K.; Wu, M-J.; Prigden, L.N. Tetrahedron Lett. 1993, 34, 47-50) to complement more traditional reactions such as reductive amination of β-ketoesters.

The racemic beta-alkyl beta amino esters can also c nveniently be prepared fr m the corresp nding beta lactam by treatment with anhydrous HCl gas in ethanol. The beta lactams were prepared from the corresponding

alkene and chlorosulfonyl isocyanate (Szabo, W.A. Aldrichimica Acta, 1977, 23 and references cited therein). Th latt r method is useful for the preparation of α and β-substituted β-aminoacids. (Manhas, M.S.; Wagle, D.R.; Chong, J.; Bose, A.K. Heterocycles, 1988, 27, 1755.) Another route to α-substituted β-aminoacids is the Raney Nickel reduction of cyanoacetic esters at temperatures ranging between 20 and 80°C and at 20 to 100 atm pressure (Testa, E.; Fontanella, L.; Fava, F. Fermaco Ed. Sci., 1958, 13, 152; Testa, E.; Fontanella, L. Annalen 1959, 625, 95). Also, a number of procedures are available for the preparation of β-aminoacids by reduction of hydrazones of keto-acids (Gootijes, J.; Nomte, W.Th. Rec. Trav. Chem. 1953, 72, 721), oximes (Anziegin, A.; Gulewivich, W. Z. Physiol. Chem., 1926, 158, 32) and nitropropionic acids. Purification of final compounds is usually by reverse phase high performance liquid chromatography (RP HPLC)[High Performance Liquid Chromatography Protein and Peptide Chemistry, F. Lottspeich, A. Henscher, K.P. Hupa, (eds.) Walter DeGruyter, New York, 1981] or crystallization.

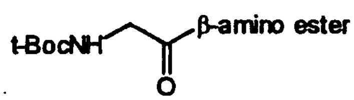
SCHEME II


t-BocNH CO2H + ClCO2
(1)
O N—CH3
DMF
(2) (A) + NMM in DMF
CO2Et
t-Boc-NH NH
O
N
HCl/Dioxane
CO2Et
H2N NH
O
N
·2HCl

(B)

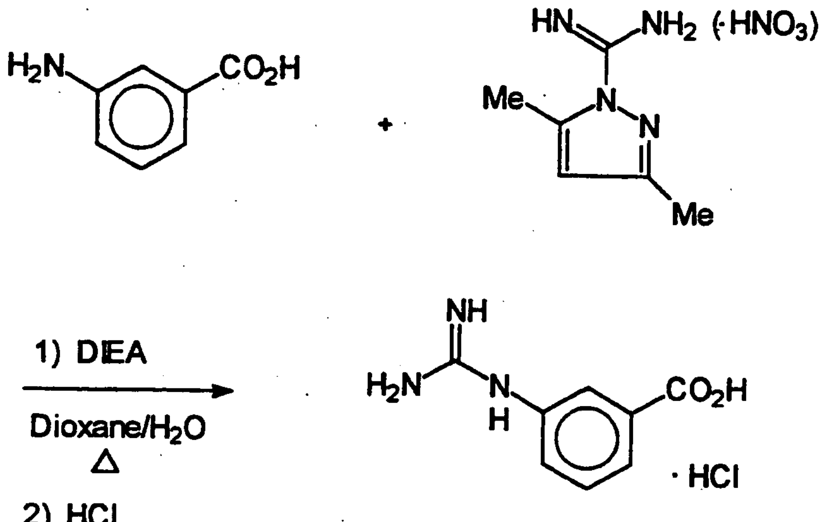
Scheme II is illustrative of methodology useful for coupling an α-amino acid to th β-amino acid compounds prepared in Scheme I. The compounds thus prepared are useful for coupling to substituted benzoic acid compounds to prepare the desired compounds of the present invention. Such methodology can be modified using conventional methodology to couple other aminoalkyl acids to the β-amino esters prepared in Scheme I.

Briefly, in Scheme II, to a solution of t-Boc-glycine in DMF is added N-methylmorpholine followed by isobutylchloroformate. In a separate flask, the substituted β-amino ester in DMF is mixed with N-methylmorpholine. The two mixtures are combined and stirred at room temperature to yield



The resulting product is deprotected using HCl/Dioxane to give (B).

SCHEME III

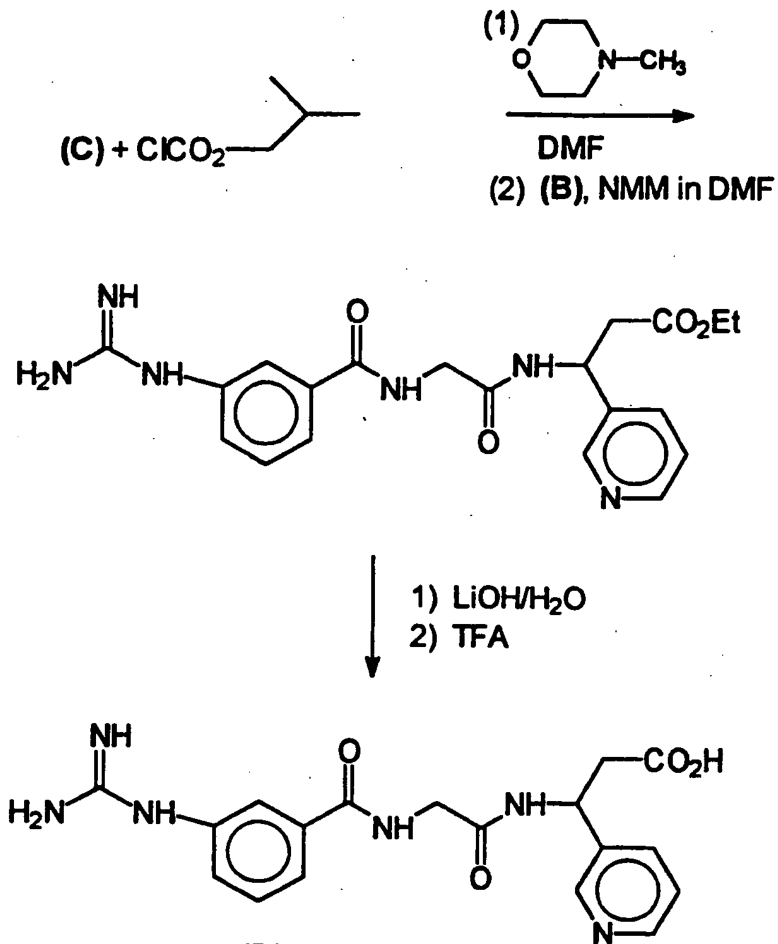

H2N
CO2H
+
HN
NH2 (·HNO3)
Me
N
N
Me
1) DIEA
Dioxane/H2O
Δ
2) HCl
NH
H2N
N
H
CO2H
· HCl

(C)

Scheme III is illustrative of methodology useful for preparing the guanidinobenz ic acid portion of the present invention which can be us d for coupling to th gly-β-amino acid. This can also be accomplished using other appropriate guanidating reagents known to those skilled in the art for example using pyrazole-carboxamidine•HCl (Aldrich). The methodology of Scheme III can be modified using conventional techniques and methods to prepare alternate compounds useful for coupling to the β-amino acids.

Briefly, in Scheme III, to 3,5-dimethylpyrazole-1-carboxamidine nitrate in dioxane, water and DIEA, is added 3-aminobenzoic acid. The mixture is stirred at reflux, the precipitate filtered, washed and dried. The precipitate is then further slurried in water, acidified with HCl and concentrated. The solvent is removed and the residue slurried in ether and dried to yield 3-guanidinobenzoic acid hydrochloride (C).

SCHEME IV



(D)

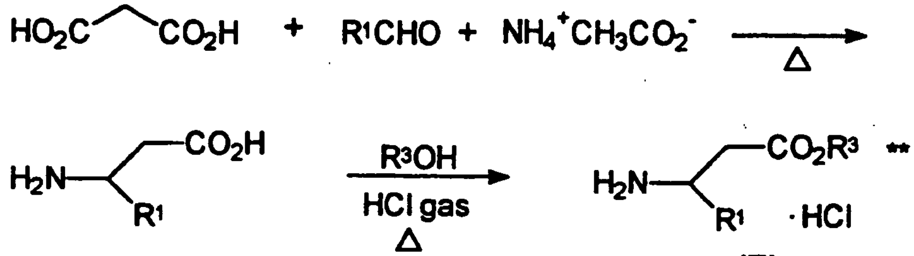
·2TFA

Scheme IV illustrates methodology useful for coupling th guanidinobenz ic acid **(C)** to the β-amino ester **(B)** porti n of the d sired comp unds of the present invention. Such methodology can be modified using conventional methods known to those having ordinary skill in the art.

Briefly, in Scheme IV to the 3-guanidinobenzoic acid **(C)** (prepared in Scheme III) in DMF and N-methylmorpholine was added isobutylchloroformate. The reaction was stirred and a slurry of the β-amino ester compound **(B)** (prepared in Scheme II) in DMF and N-methylmorpholine was added portionwise. The reaction was stirred, the precipitate filtered and washed with DMF. The DMF was removed. The resulting ester is dissolved in water, washed with ether and LiOH is added to the aqueous layer and stirred for approximately 1 hour. The solution is treated with trifluoroacetic acid to pH=5 and the product purified by RPHPLC to yield the desired compounds **(D)**.

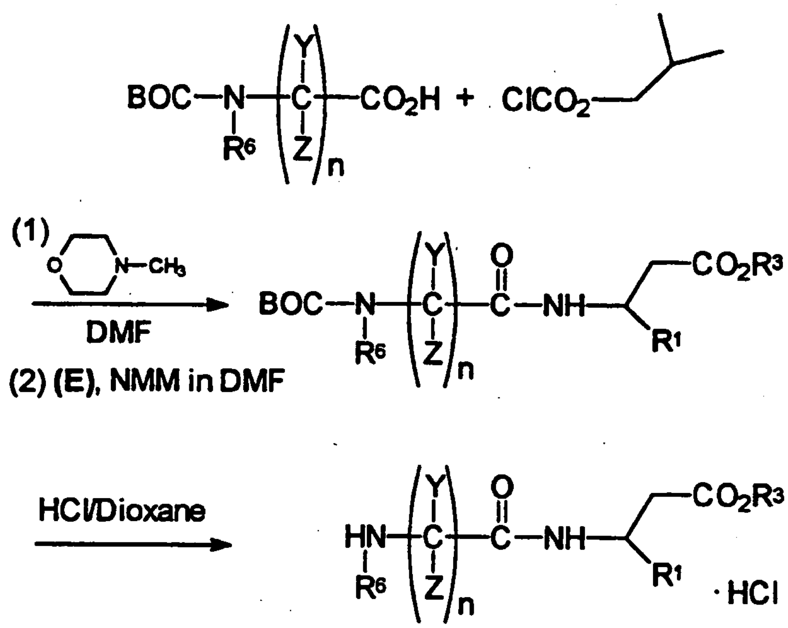
SCHEME V

Step A



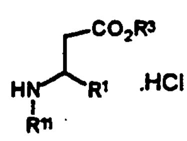
(E)

Step B



(F)

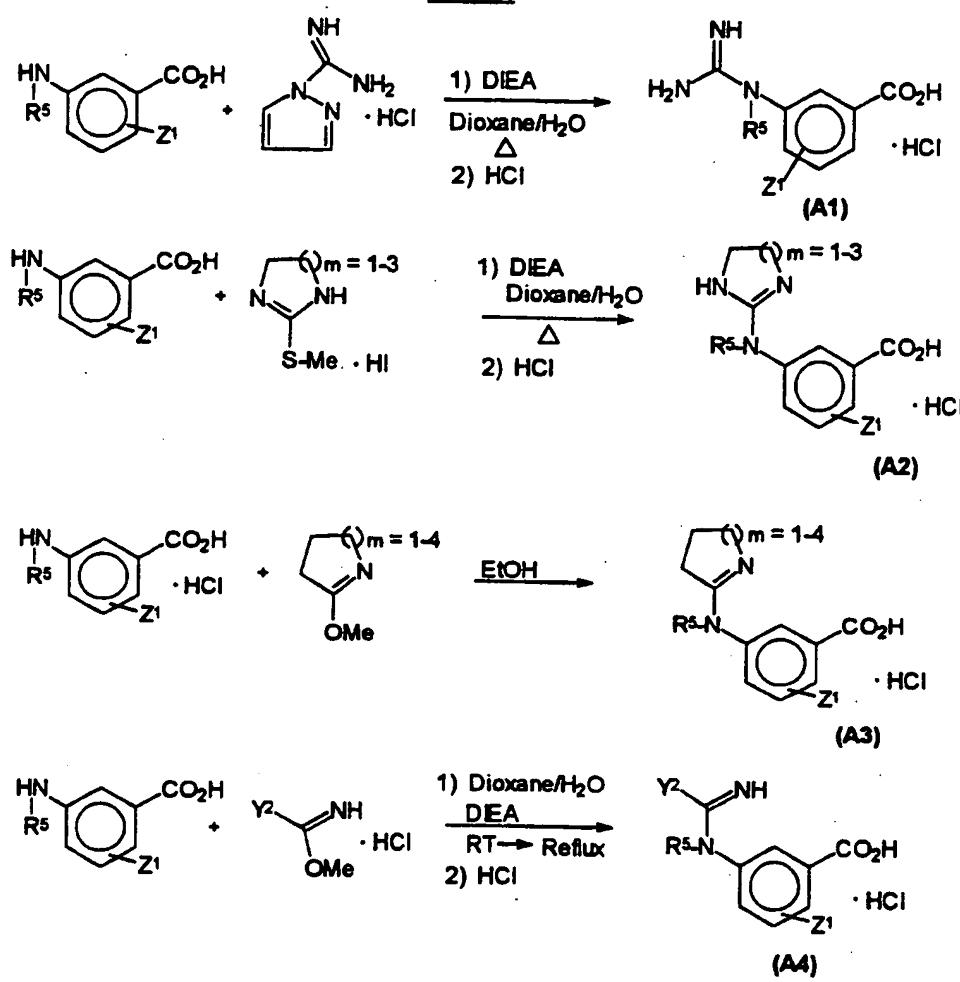
** If R^{11} is not H, alkylation is performed at this point of the reaction using standard alkylating procedures to form



which can be used instead of (E) in the synthetic methods herein.

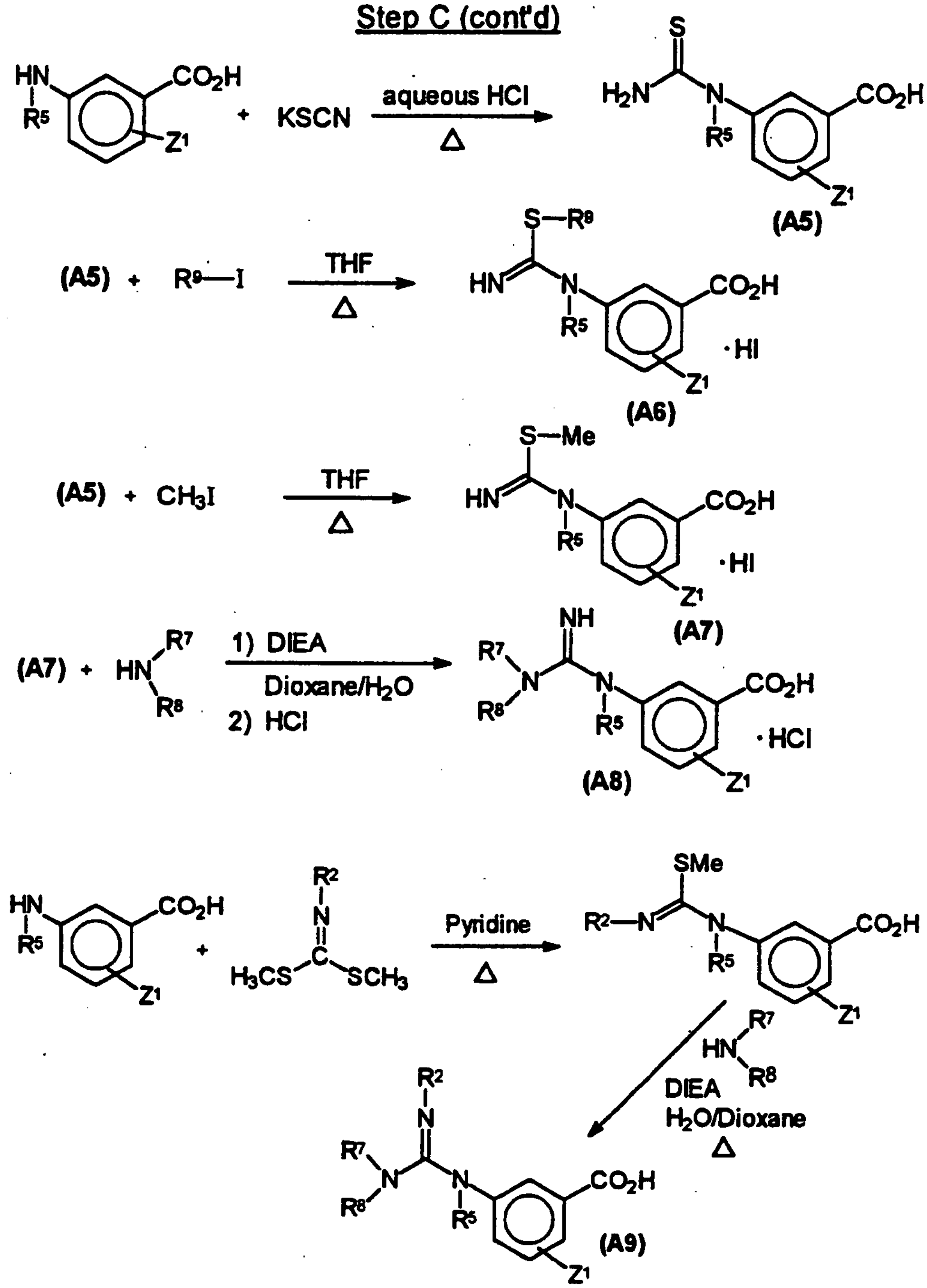
SCHEME V (Cont'd)

St p C



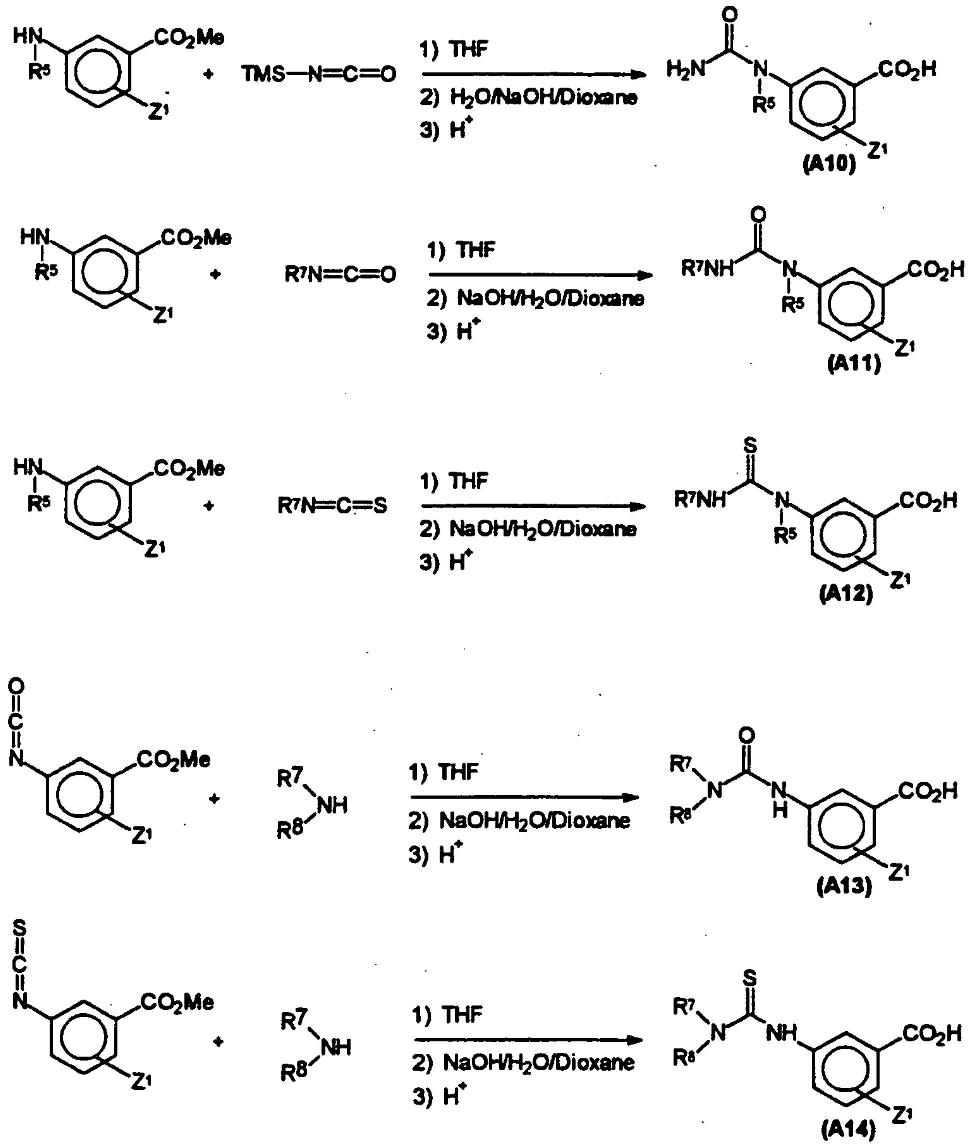
SCHEME V (Cont'd)

Step C (cont'd)



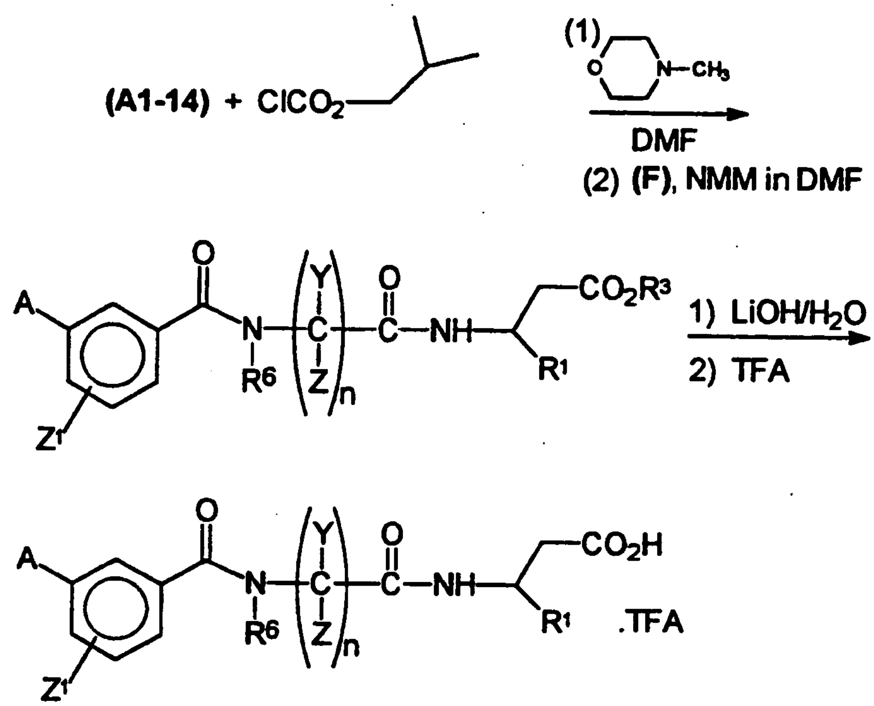
SCHEME V (Cont'd)

Step C (cont'd)



SCHEME V (Cont'd)

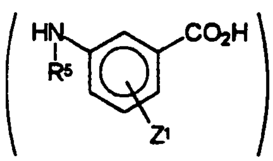
Step D



Scheme V is illustrative of methodology useful for preparing various compounds of the present invention. Such methodology is more specifically defined in the following examples and in Schemes I-IV. Such methodology can be modified by one skilled in the art, substituting known reagents and conditions from conventional methodology to produce the desired compounds.

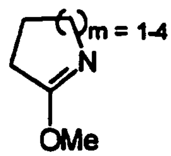
Specifically, in Scheme V, Step C:

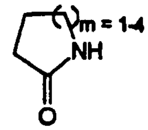
In the synthesis of intermediate benzoic acids **(A1)** through **(A14)**, the starting amino benzoic acids

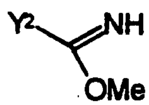


are either commercially available or can be converted to such amino benzoic acids via reduction of the corresponding nitro benzoic acid, which can be obtained commercially or syntheized by nitration of the appropriate benzoic acid, followed by reduction to the desired amino benzoic acid. These are all when R^5 is H. If R^5 is other than H, alkylation of the amino functionality can be achieved by conventional methodology.

Furthermore, synthesis of intermediate **(A2)** can also be accomplished as disclosed generally in US 3,202,660, starting with the appropriate amino benzoic acid.

 used in the synthesis f intermediates **(A3)**,

can be synthesized from  and $(Me)_3OBF_4$ in dichloromethane.

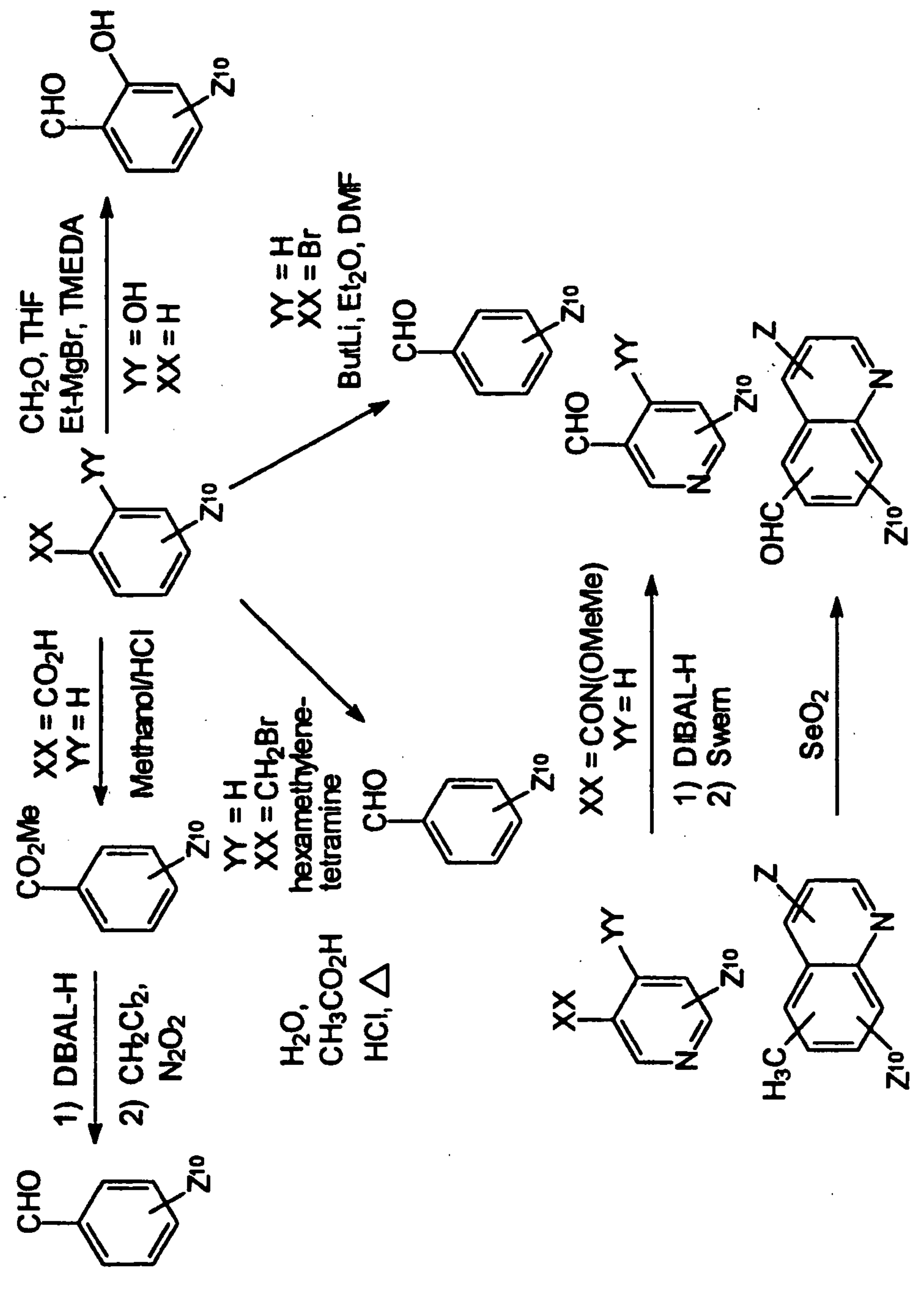
 ·HCl used in the synthesis of intermediate **(A4)**, can be synthesized from Y^2-CN and MeOH (1 equivalent) and HCl gas (1 equivalent) in heptane.

All other reagents in Scheme V are either commercially available or readily synthesized by methodologies known by those skilled in the art.

Coupling of the intermediates from Scheme V, Step C [**(A1)** through **(A14)**] with the intermediate **(F)** (from Scheme V Step B) can be accomplished using other coupling reagents known to those skilled in the art in addition to the mixed anhydride method described in Scheme V Step D, to give the final desired products.

SCHEME VA

Alternate synthesis of aldehydes

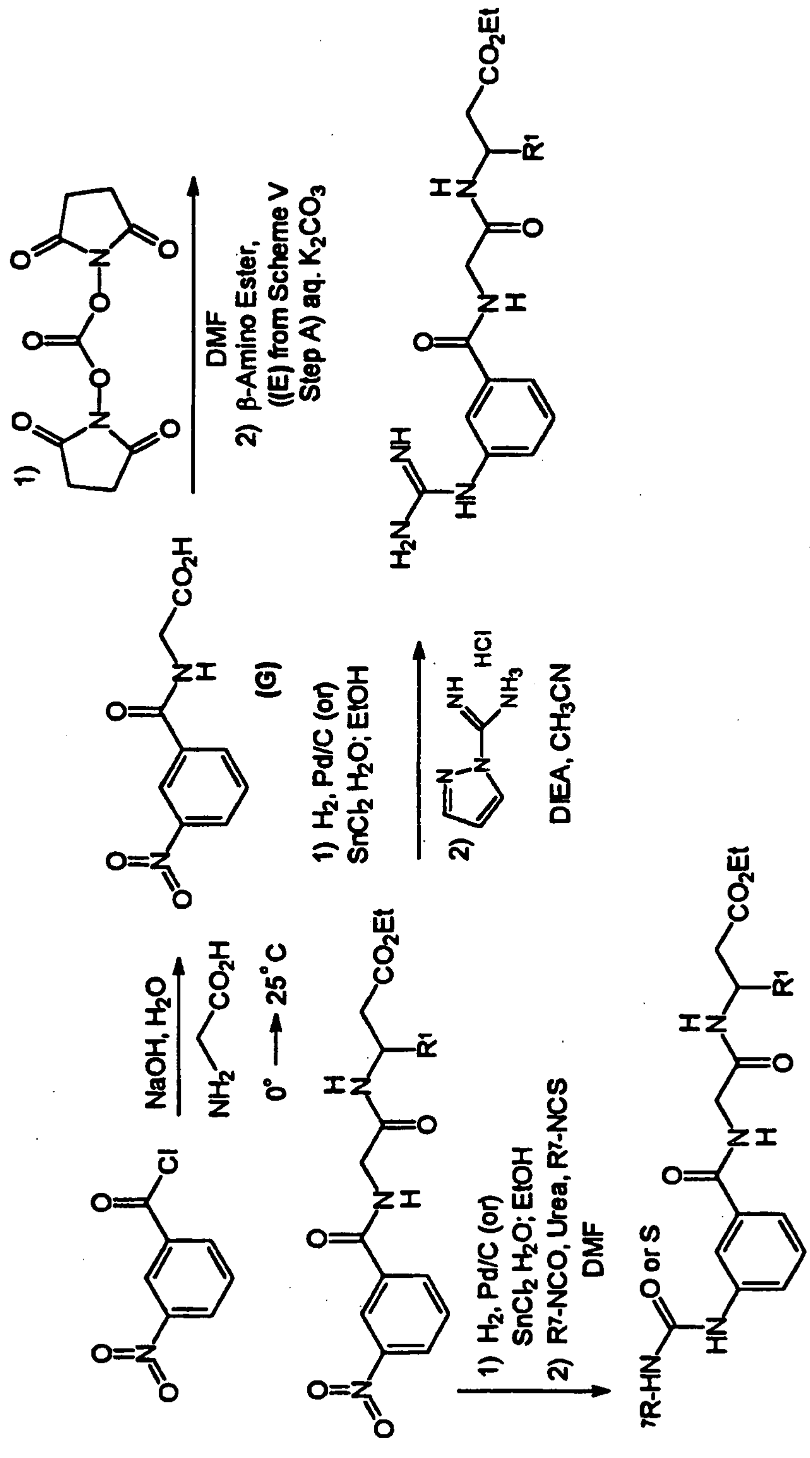


Z^{10} is defined the same as Z^1

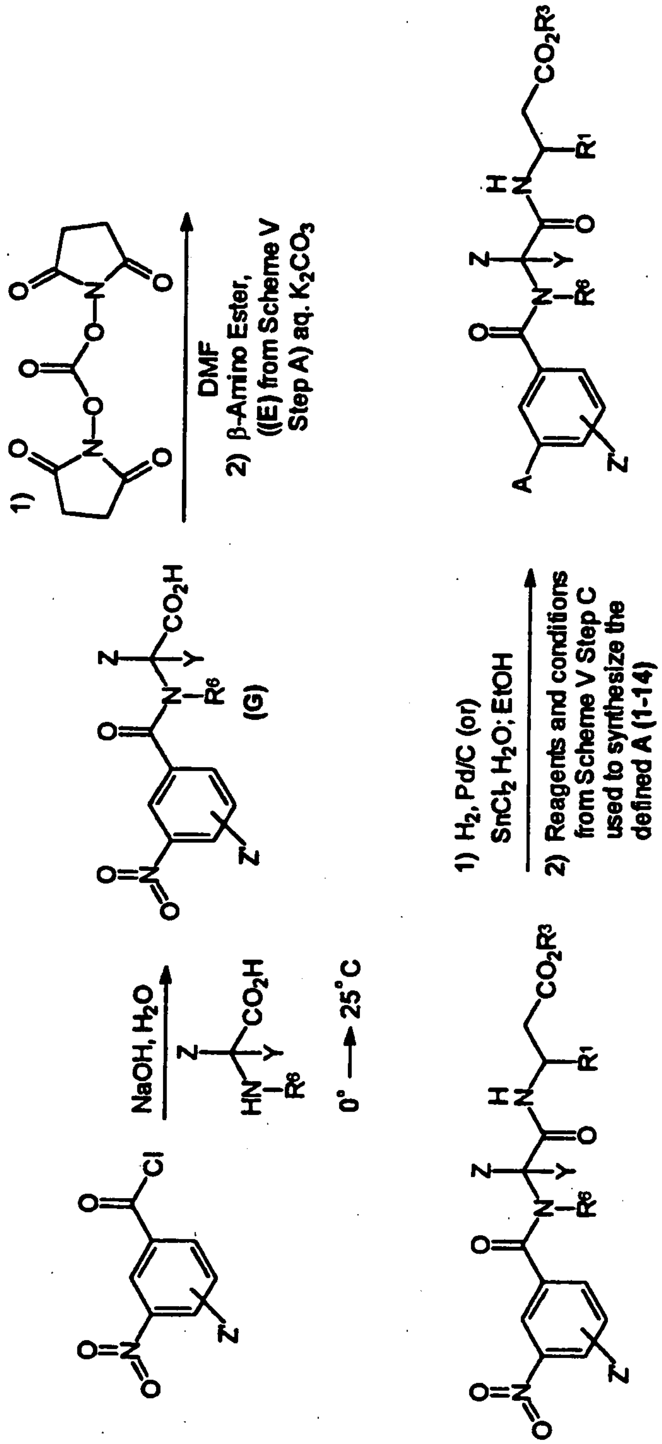
Scheme VA is illustrative of meth dology useful for th preparation of aldehydes (R^1) which are not commercially available, and are used in the preparation of β-amino acids as in Scheme V, Step A. Such β-amino acids are then further used to synthesize the compounds of the present invention as further exemplified in Scheme V, Steps A through D.

Other such methodologies known to those skilled in the art are available and can also be used to synthesize aldehydes useful in preparing compounds of the present invention.

SCHEME VI (A)


NaOH, H2O
0° → 25°C
(G)
1) H2, Pd/C (or) SnCl2 H2O; EtOH
2) DIEA, CH3CN
1) DMF
2) β-Amino Ester, ((E) from Scheme V Step A) aq. K2CO3
1) H2, Pd/C (or) SnCl2 H2O; EtOH
2) R7-NCO, Urea, R7-NCS DMF
O or S

SCHEME VI (B)


NaOH, H_2O
0° ⟶ 25° C
(G)
DMF
2) β-Amino Ester,
((E) from Scheme V
Step A) aq. K_2CO_3
1) H_2, Pd/C (or)
$SnCl_2$ H_2O; EtOH
2) Reagents and conditions
from Scheme V Step C
used to synthesize the
defined A (1-14)

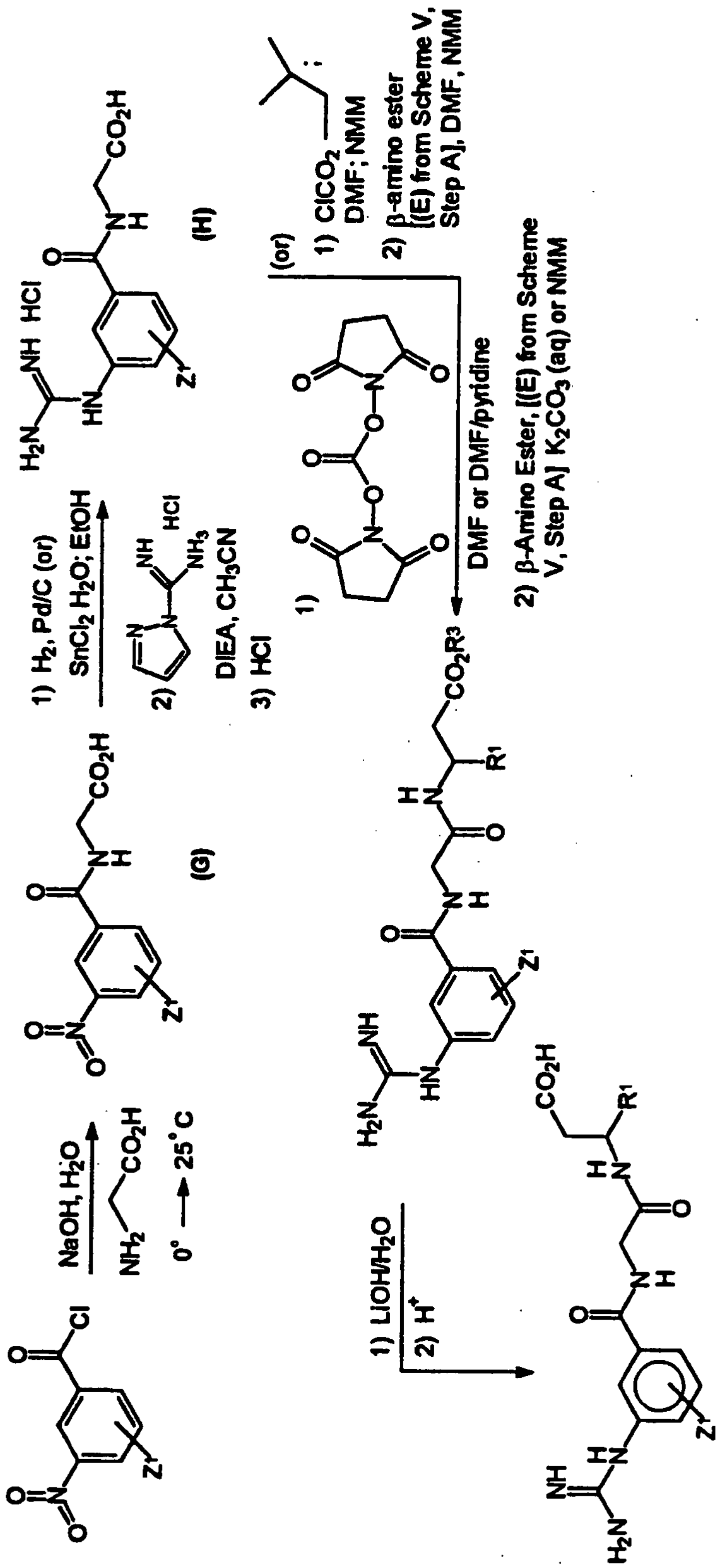
Schem VI(A) r pr sents an alternative method of synthesis of the compounds of the Formula I. All reagents are either commercially available or ar mad via methods known to those skilled in the art.

The synthesis of β-amino esters is as described for Compound **(E)** in Scheme V, Step A.

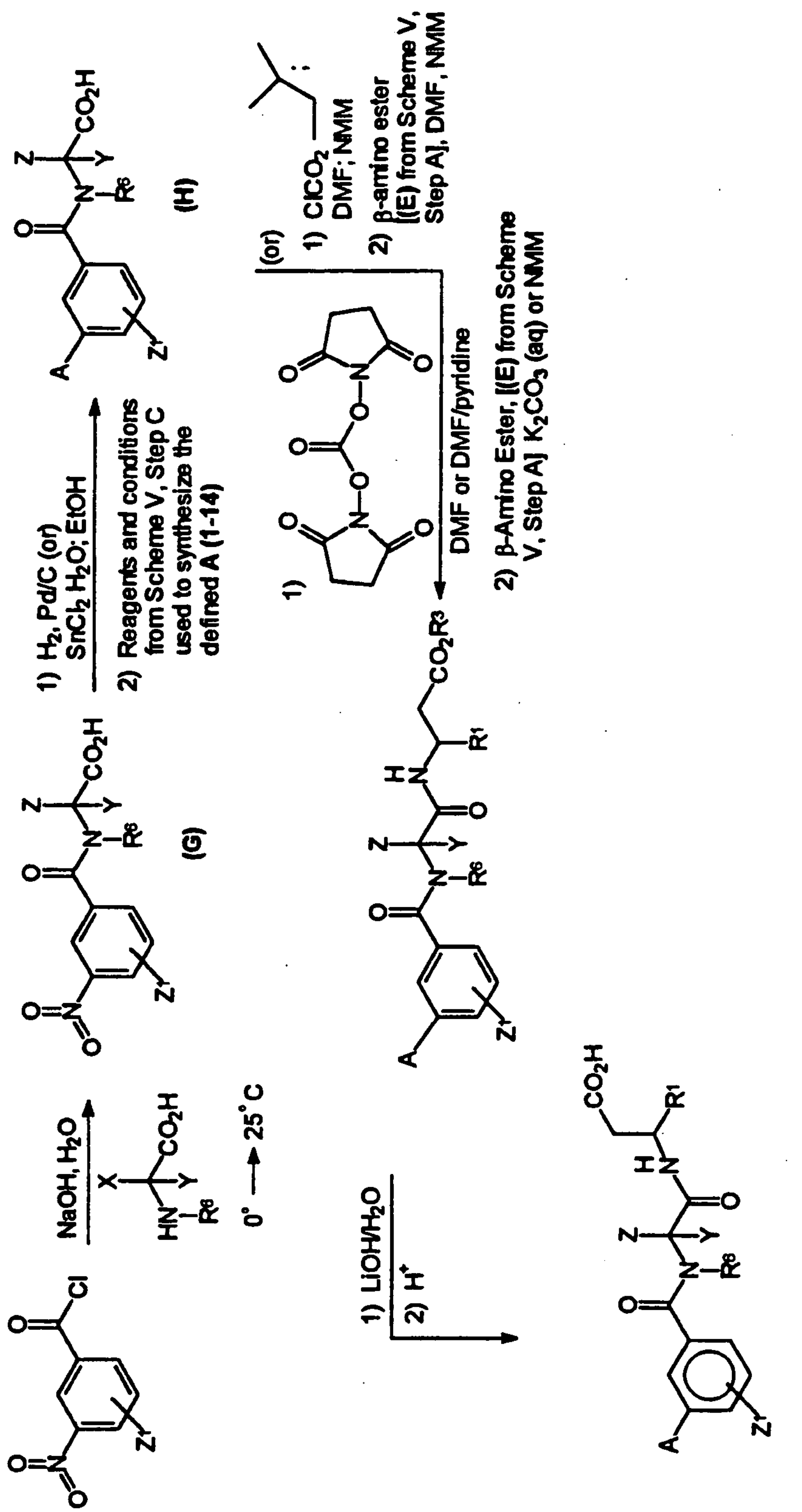
Alternative methods of coupling, guanidation or formation of ureas and thioureas can be used and are readily known to those skilled in the art.

Scheme VI(B) represents another alternative synthesis of the compounds of the present invention. All reagents are either commercially available or are made via standard and known methodologies.

SCHEME VII(A)

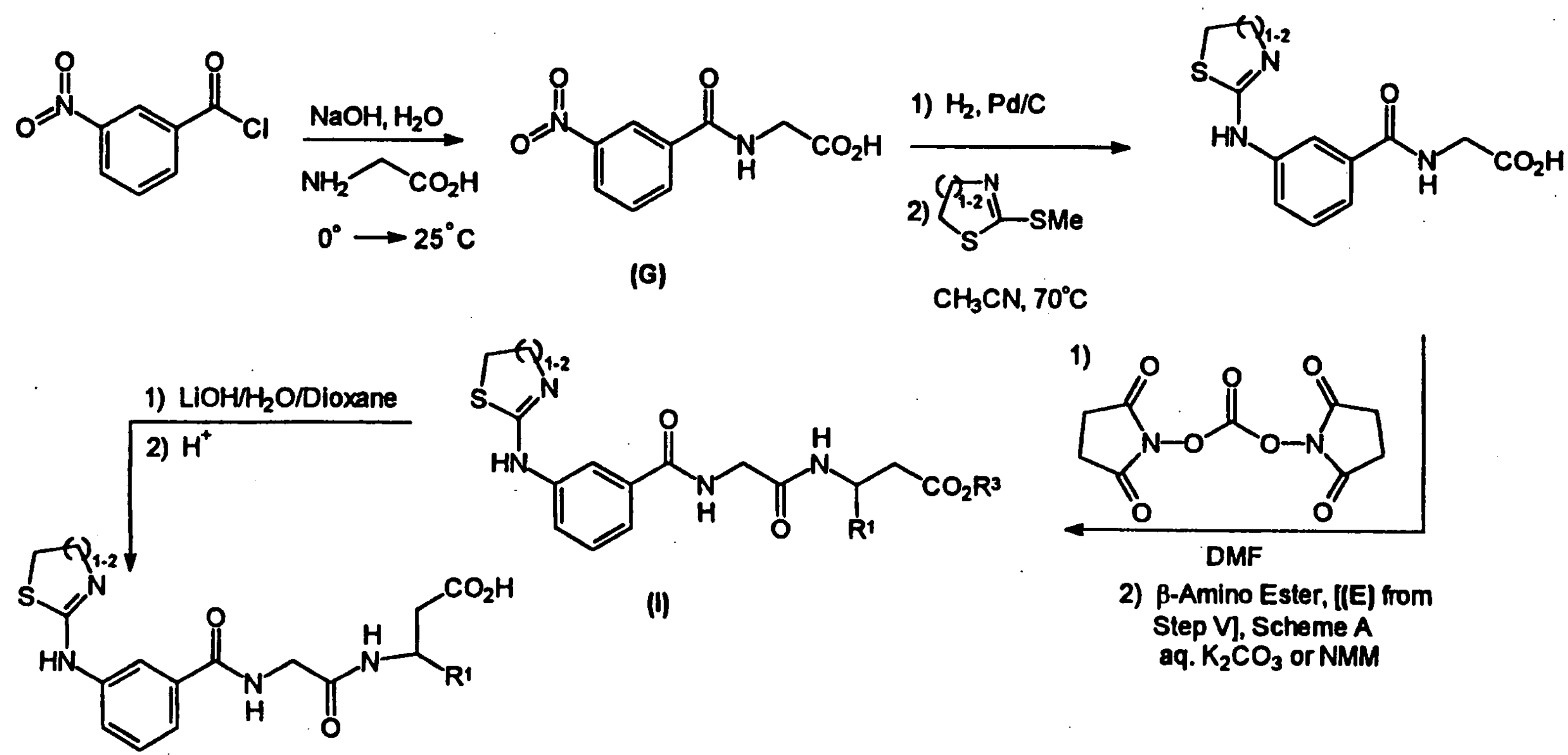


SCHEME VII(B)


NaOH, H2O
0° → 25°C
(G)
1) H2, Pd/C (or) SnCl2 H2O; EtOH
2) Reagents and conditions from Scheme V, Step C used to synthesize the defined A (1-14)
(H)
(or)
1) ClCO2 DMF; NMM
2) β-amino ester [(E) from Scheme V, Step A], DMF, NMM
1) DMF or DMF/pyridine
2) β-Amino Ester, [(E) from Scheme V, Step A] K2CO3 (aq) or NMM
1) LiOH/H2O
2) H+

Schemes VII(A) and (B) are similar to Schemes VI(A) and (B) and provide additional meth ds of synthesis of c mpounds of the present invention. (Scheme VIIB being a more general scheme than Scheme VIIA.) As in Scheme VI, reagents and conditions are not restricted to those defined in these schemes but may be substituted for with alternative reagents known to those skilled in the art.

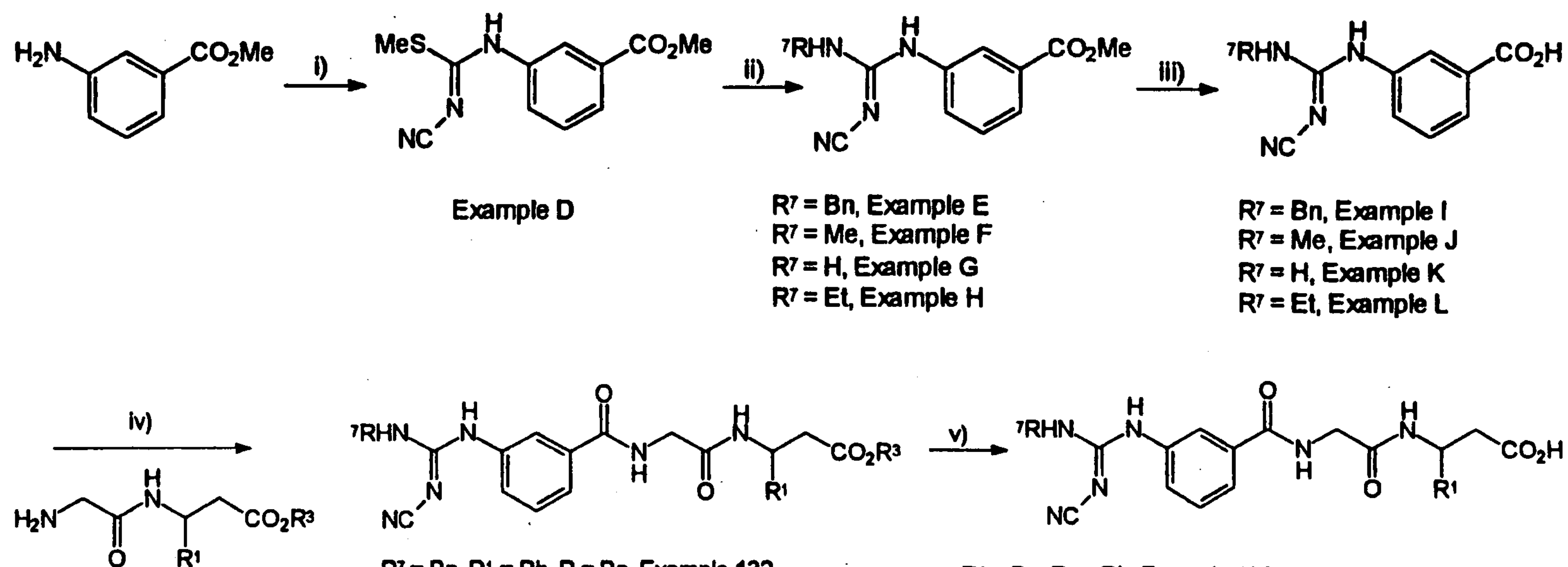
SCHEME VIII


NaOH, H_2O
NH_2 CO_2H
0° → 25°C
(G)
1) H_2, Pd/C
2) SMe
CH_3CN, 70°C
1)
DMF
2) β-Amino Ester, [(E) from Step V], Scheme A
aq. K_2CO_3 or NMM
(I)
1) LiOH/H_2O/Dioxane
2) H^+

Scheme VIII is illustrative of the synthesis used to form group A in the general Formula I where A is an aminothiazoline or aminothiazine. All starting materials and reagents are commercially available or are defined elsewhere in the enclosed Schemes and Examples. Alternative methods of coupling or alternative reagents and conditions may be employed as are known to those skilled in the art.

SCHEME IX

Cyanoguanidines



Example D

R^7 = Bn, Example E
R^7 = Me, Example F
R^7 = H, Example G
R^7 = Et, Example H

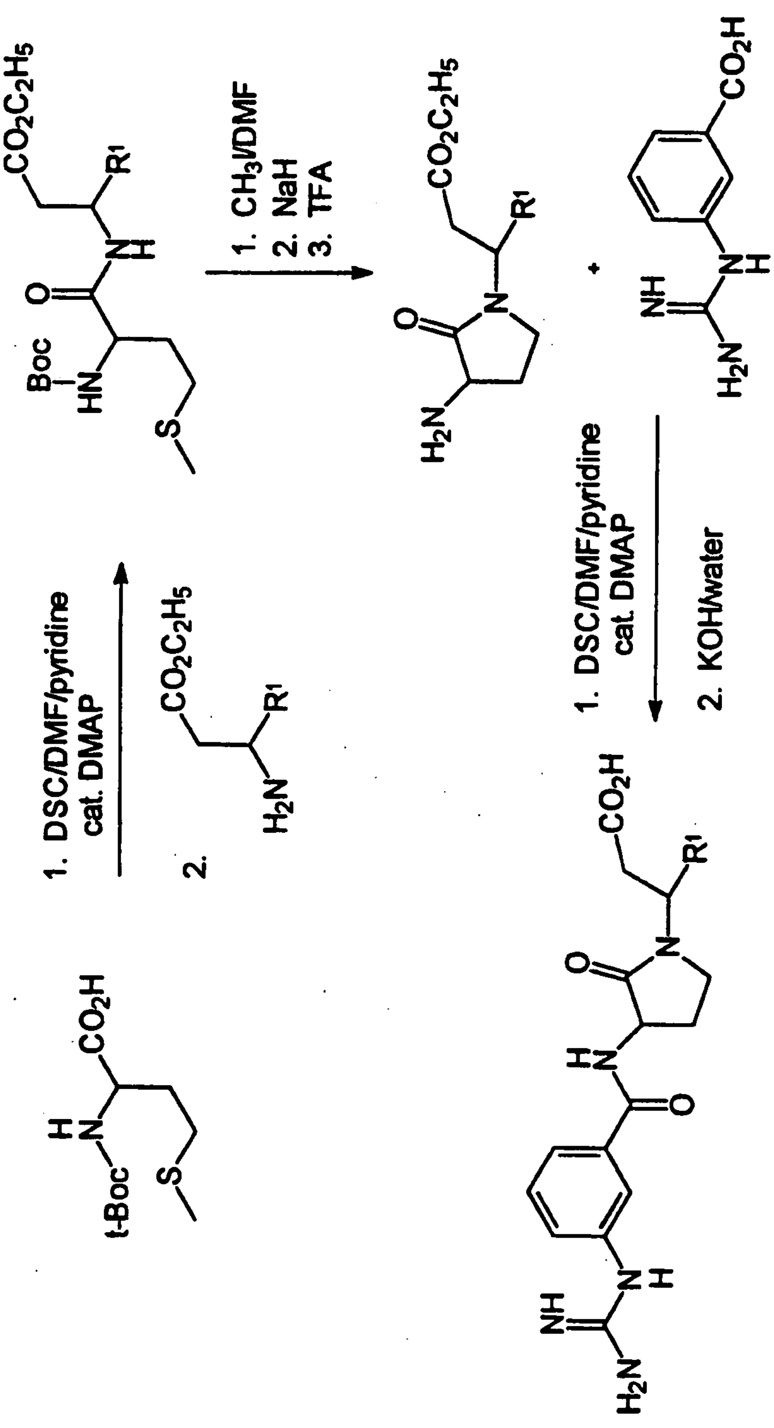
R^7 = Bn, Example I
R^7 = Me, Example J
R^7 = H, Example K
R^7 = Et, Example L

R^7 = Bn, R^1 = Ph, R = Bn, Example 132
R^7 = Me, R^1 = Ph, R = Bn, Example 133
R^7 = H, R^1 = Ph, R = Bn, Example 134
R^7 = Et, R^1 = Ph, R = Et, Example 135
R^7 = Me, R^1 = Acetylene, R = Et, Example 140

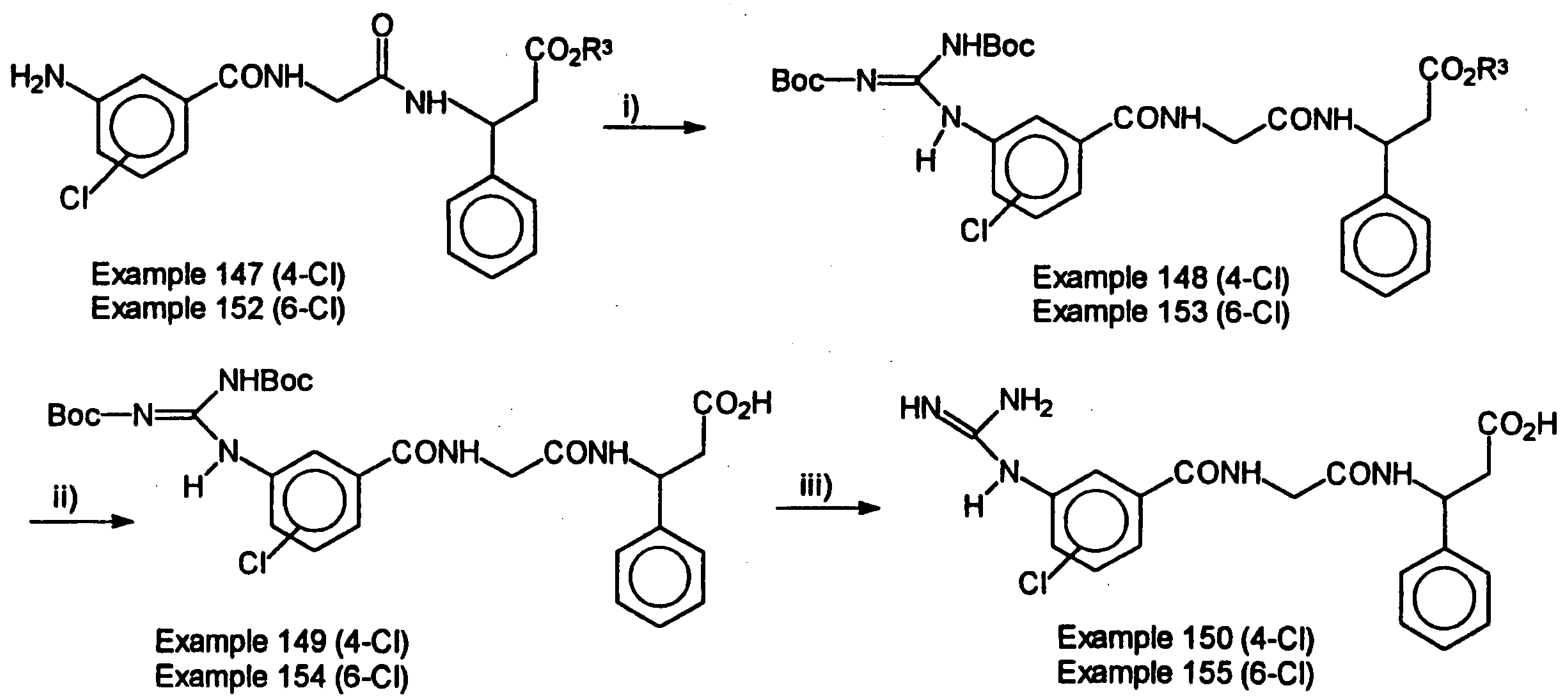
R^7 = Bn, R^1 = Ph, Example 136
R^7 = Me, R^1 = Ph, Example 137
R^7 = H, R^1 = Ph, Example 138
R^7 = Et, R^1 = Ph, Example 139
R^7 = Me, R^1 = Acetylene, Example 141

i) Pyridine, Dimethyl N-cyanodithioiminocarbonate, 70°C. ii) R^7NH_2, EtOH, Reflux. iii) THF, MeOH, H_2O, NaOH.
iv) CH_2Cl_2, DMAP, NEt_3, EDCl. v) 1) THF, MeOH, H_2O, NaOH 2) H^+.

SCHEME X


1. DSC/DMF/pyridine
cat. DMAP
2.
1. CH$_3$I/DMF
2. NaH
3. TFA
1. DSC/DMF/pyridine
cat. DMAP
2. KOH/water

SCHEME XI



i) N,N1-Bis-Boc-thiourea, DMF, NEt_3, $HgCl_2$, 0 , 15 mins.
ii) MeOH, THF, H_2O, KOH.
iii) CH_2Cl_2, TFA, 0°, 90 mins.

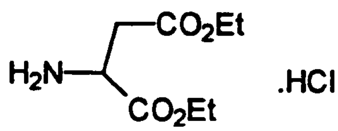
Schem s IX, X and XI are further examples of synthesis of particular c mpounds of the pres nt invention. All starting materials and reagents are commercially available or are disclosed in the present specification. Alternative methods, reagents and conditions can be employed by those skilled in the art.

<u>Scheme XII</u>

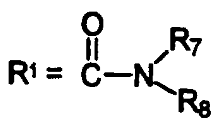
For compounds wherein

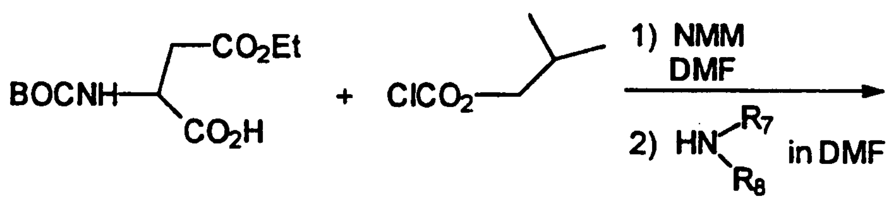
1) $R^1 = CO_2H$

(E) is the commercially available

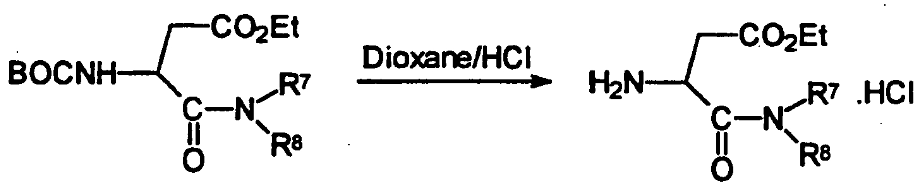


2)

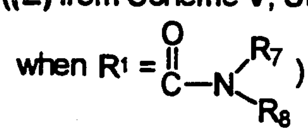


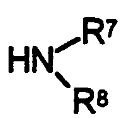


(commercially available)



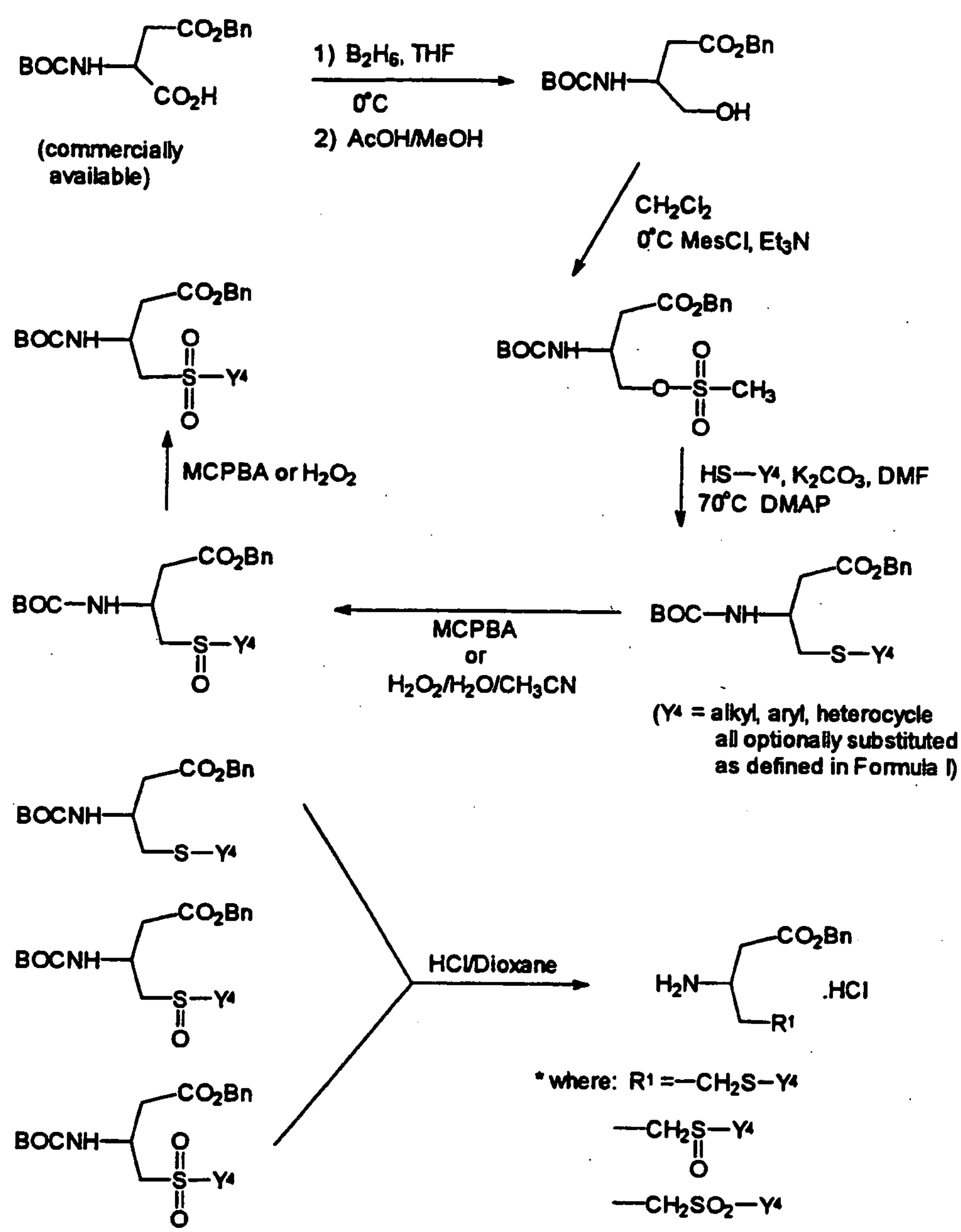
((E) from Scheme V, Step A



wherein  denotes an amino acid, the amino acid being protected with the appropriate protecting groups.

Additional methodologies for further R^1 groups are as follows:

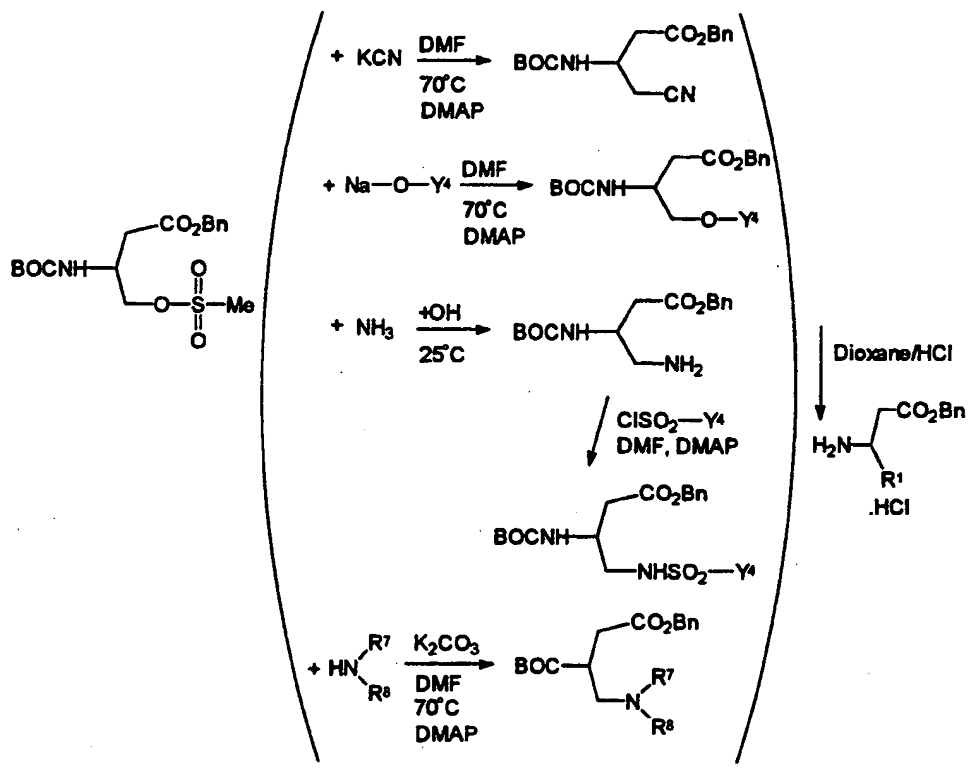
SCHEME XII (cont'd)



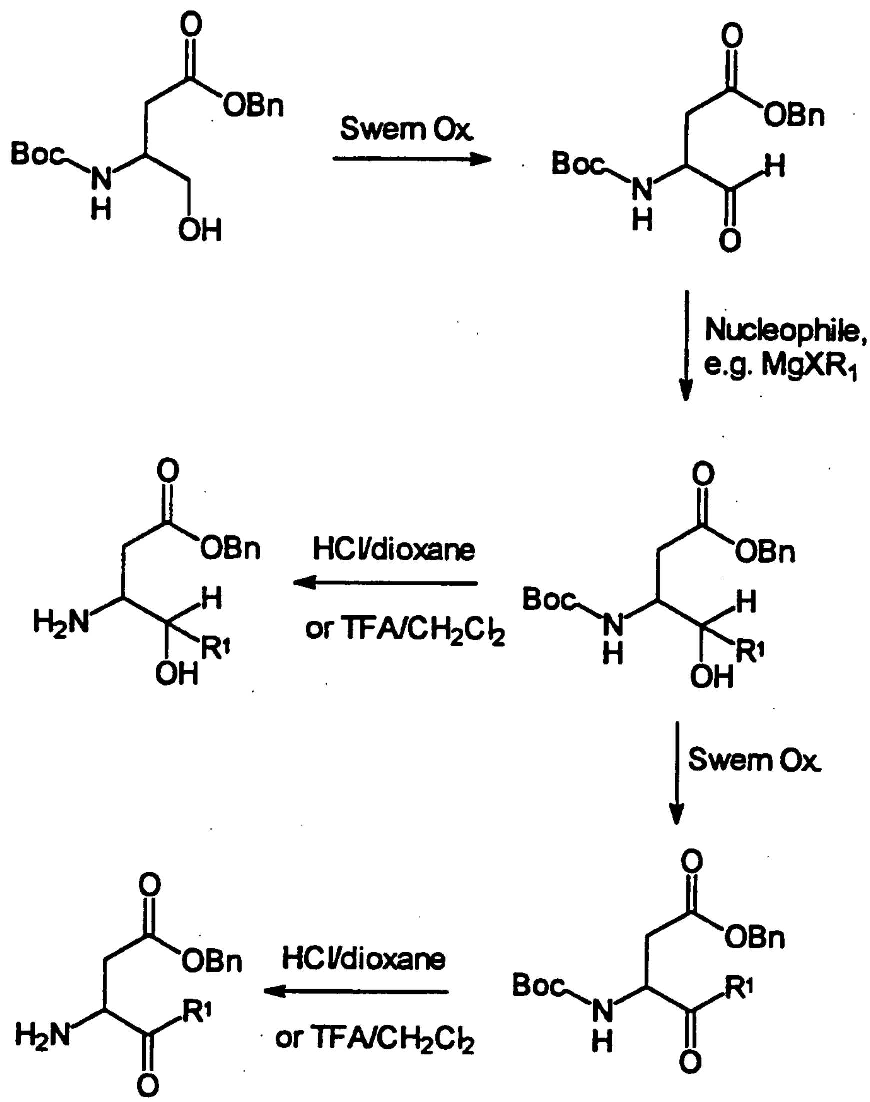
*These can all be further used as an intermediate such as (E) in the various Schemes used to exemplify the method of synthesis of the compounds of the present invention.

SCHEME XII (cont'd)

In a similar mann r, compounds of th present invention wherein R^1 is substituted alkyl can be synthesized in the following manner:



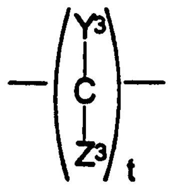
SCHEME XIIA


OBn
Boc
N
H
OH
Swern Ox
Nucleophile,
e.g. MgXR1
HCl/dioxane
or TFA/CH2Cl2
H2N
R1
Swern Ox
HCl/dioxane
or TFA/CH2Cl2

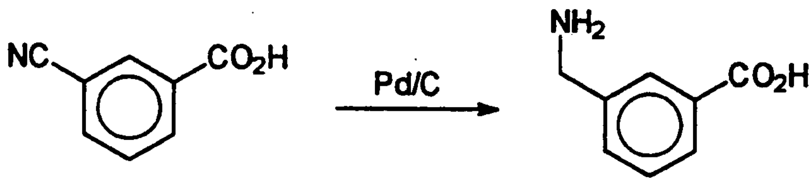
Schem XII A outlines the synthesis of protected aspartyl aldehyde from aspartyl alcohol prepared in Scheme XII using Swern oxidation procedures and elaboration of the aldehyde by reaction with a nucleophile, e.g., either a commercially available Grignard Reagent or a Grignard Reagent prepared by standard procedures, to afford the C-4, R_1-substituted aspartyl alcohol derivative. The primary amine product may be prepared by removing the BOC group by employing standard acidic conditions to provide the intermediate β-amino acids (e.g. Scheme I). The BOC protected C-4 substituted alcohol may be converted to the keto-derivative by a second Swern oxidation followed by BOC removal to give the desired intermediate amine (e.g. Scheme I).

SCHEME XIII

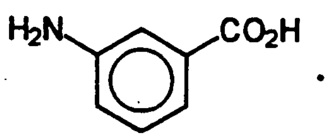
To synthesize compounds wherein



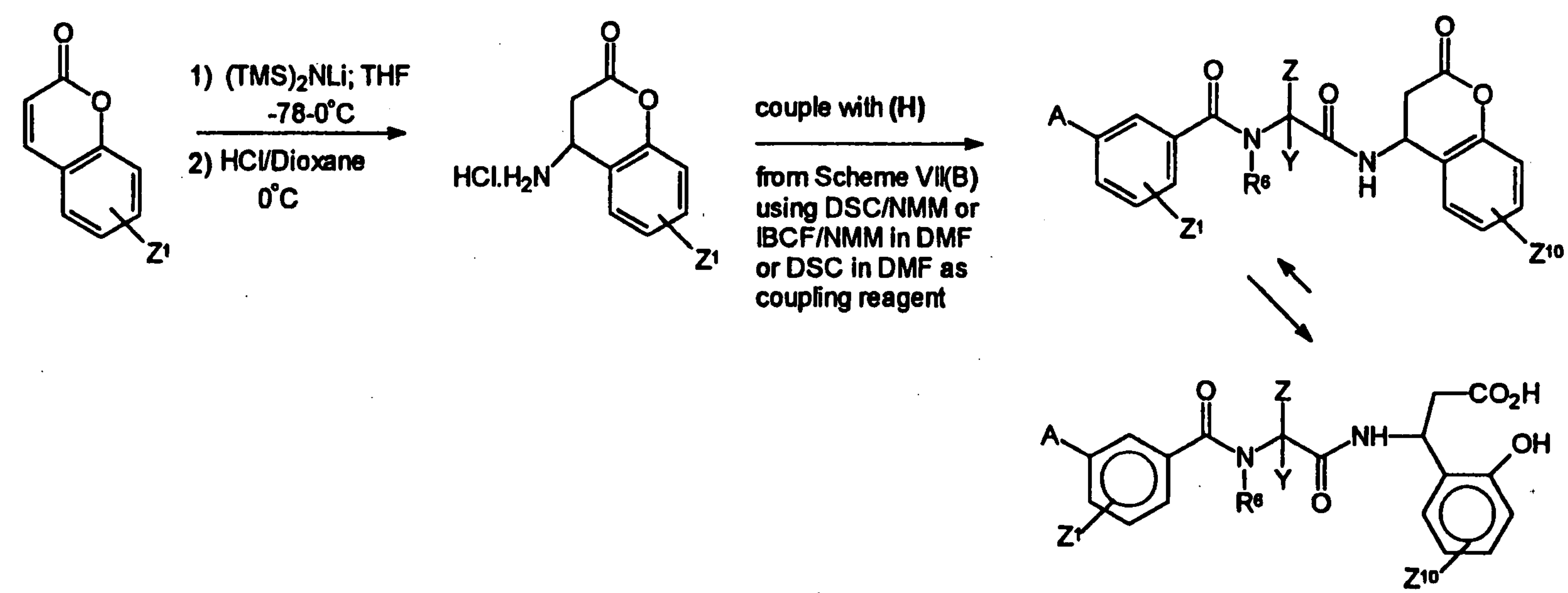
where t = 1 and Y^3 and Z^3 are both hydrogen:



which is then treated in the same manner of further derivatization as exemplified in the previous schemes for:



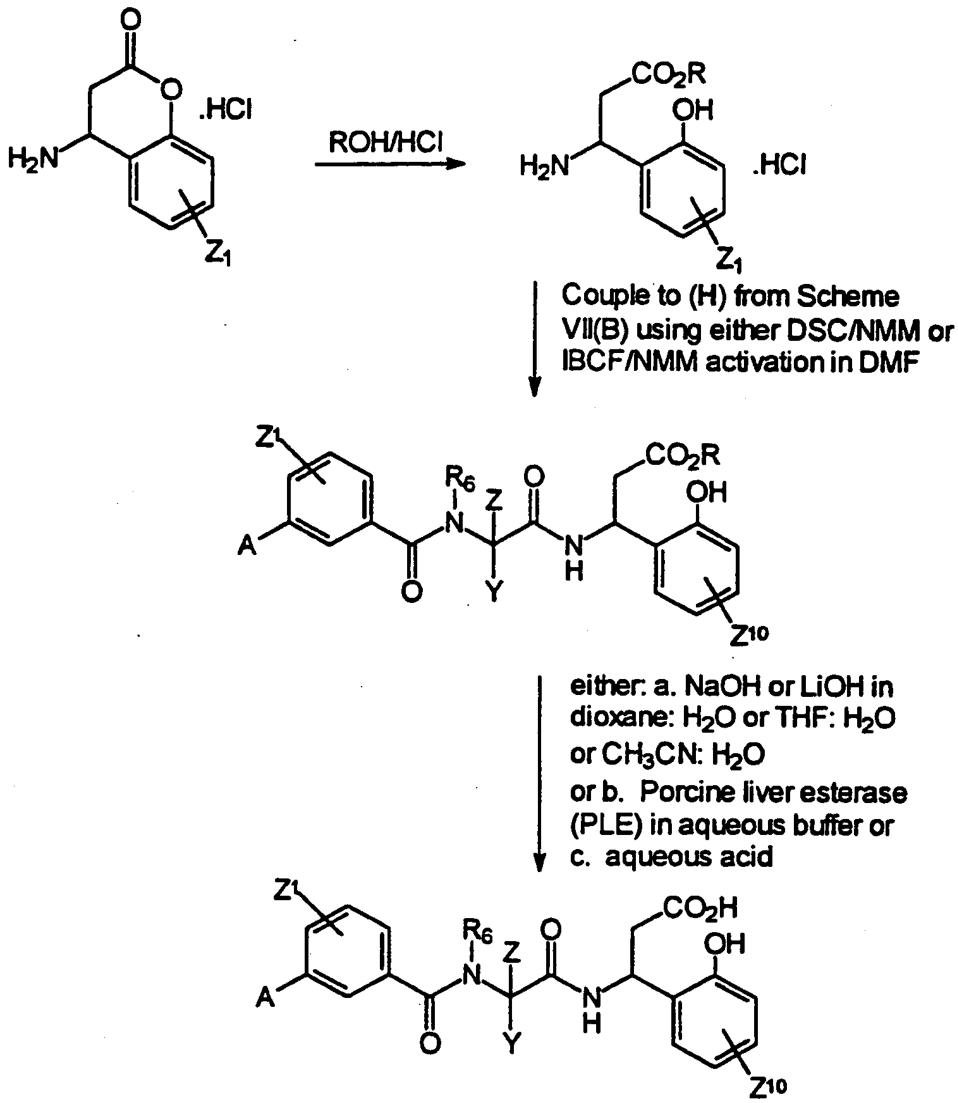
SCHEME XIV



Z^{10} is defined as in Z^{1}

Scheme XIV represents th synthesis of aminohydrocoumarins (see J. Rico, Tett. Let., 1994, 35, 6599-6602) which are readily opened t form R^1 being an orthohydroxyphenyl moiety, further substituted by Z^1.

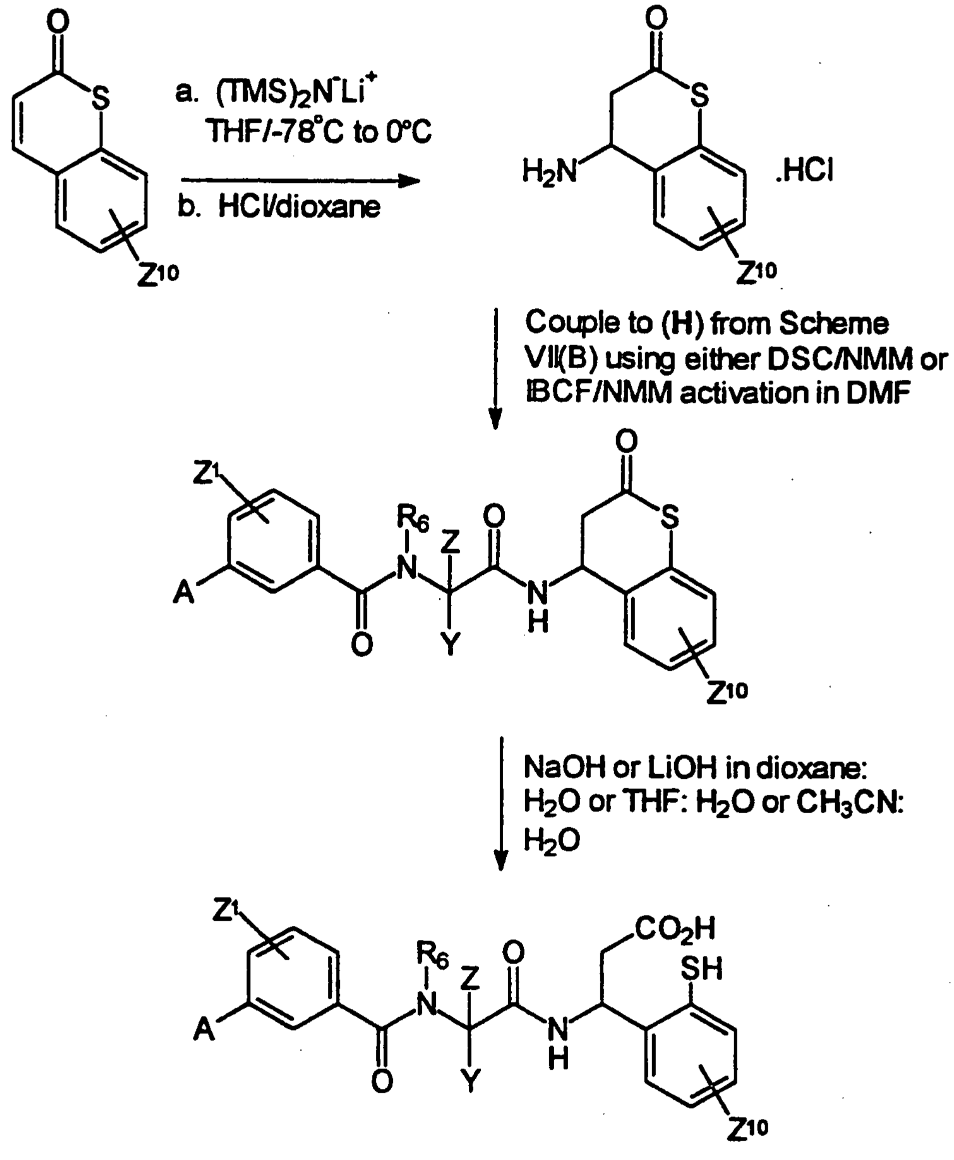
SCHEME XIV A



Z^{10} is the same as defined in Z^1

Scheme XIV A represents th synthesis of aminohydrocoumarin esters from the aminohydrocoumarins of Scheme XIV and subsequent coupling with intermediates (**H**) from Scheme VII(B) using either activation of (**H**) by DSC/NMM/DMF or IBCF/NMM/DMF followed by aminohydrocoumarin ester hydrochloride salt/NMM. Subsequent hydrolysis using standard conditions resulted in formation of the carboxylic acid derivative.

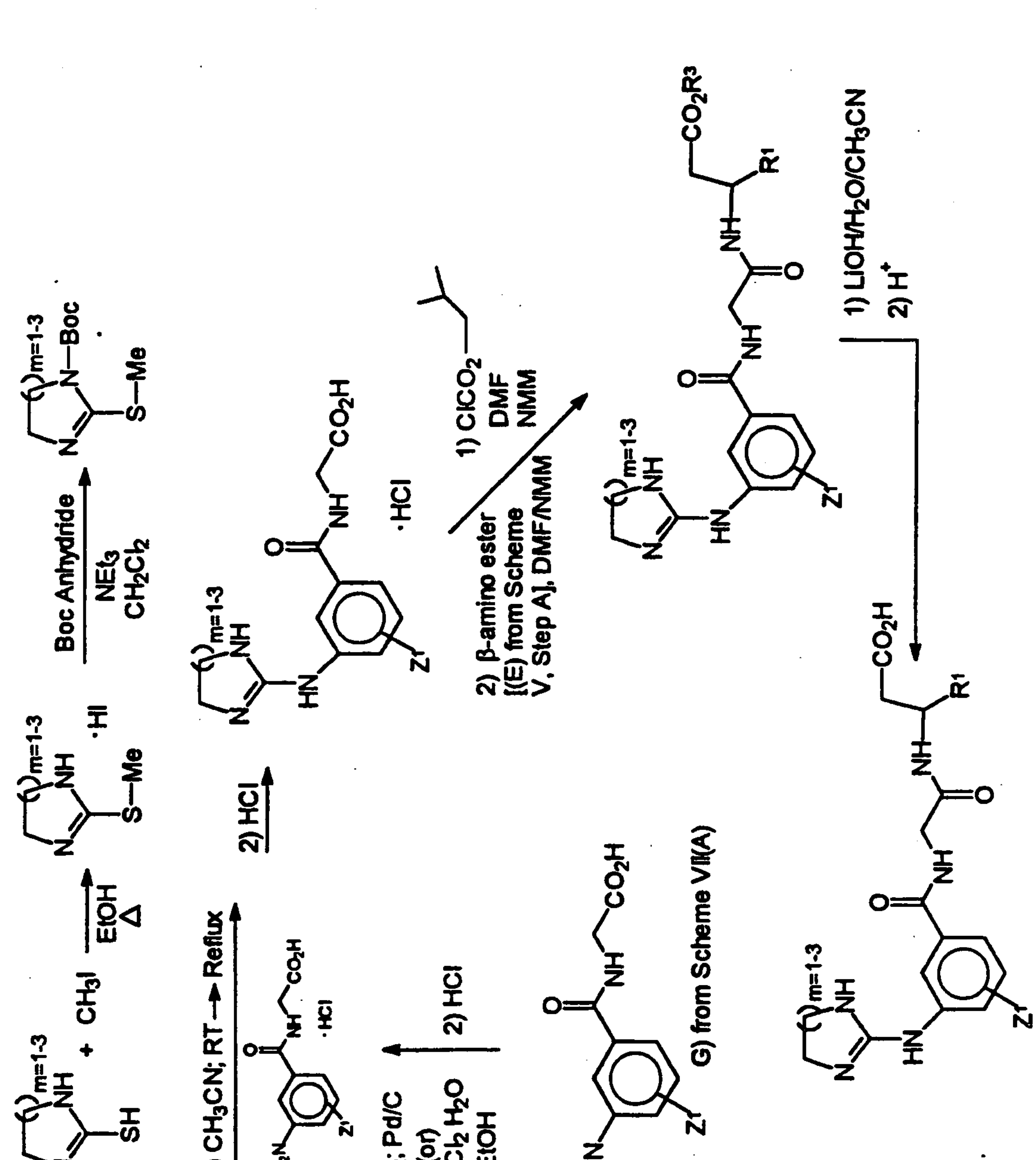
SCHEME XIV B



Z^{10} is defined the same as Z^1

Scheme XIV B represents the synthesis of 4-aminohydrothiocoumarin from thiocoumarins. Thiocoumarins are readily prepared according to J.A. Panetta and H. Rapoport, J. Org. Chem., **1982**, 47, 2626-2628 and references cited therein and may be converted to the 4-aminohydrothiocoumarin derivative according to the general procedure of Scheme XIV. Coupling of the aminohydrothiocoumarin to intermediate (H) from Scheme VII(B) can be achieved using methodology similar to Scheme XIV and XIV A. Hydrolysis to give the carboxylate-thiol product is readily achieved using a base (e.g. LiOH or NaOH) in an aqueous organic solvent.

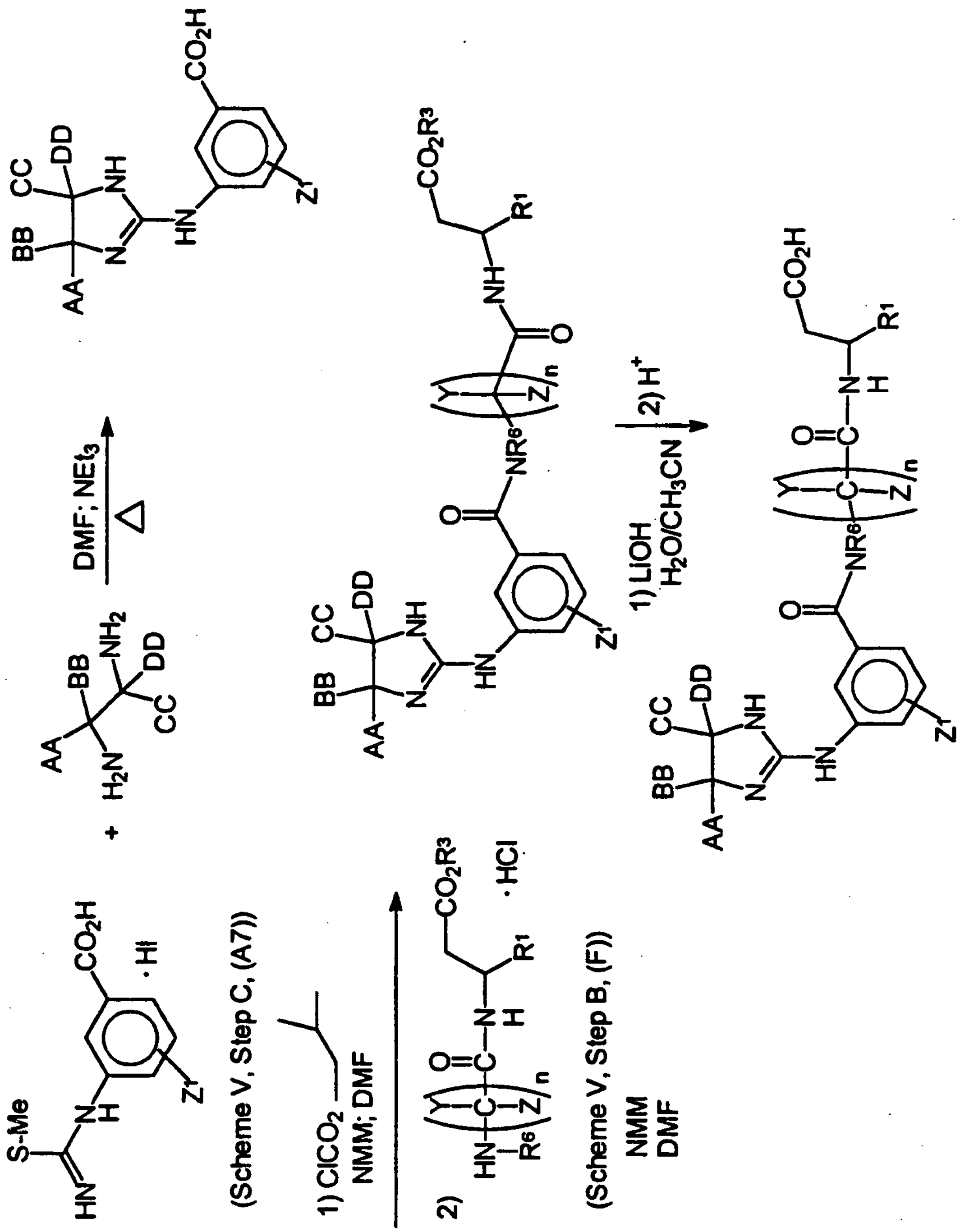
SCHEME XVI


m=1-3
SH
CH3I
EtOH
Δ
S—Me
·HI
Boc Anhydride
NEt3
CH2Cl2
N—Boc
1) CH3CN; RT → Reflux
2) HCl
CO2H
·HCl
Z1
1) H2; Pd/C
(or)
SnCl2 H2O
EtOH
2) HCl
O2N
G) from Scheme VII(A)
1) ClCO2
DMF
NMM
2) β-amino ester
[(E) from Scheme
V, Step A], DMF/NMM
CO2R3
R1
1) LiOH/H2O/CH3CN
2) H+

Scheme XVI represents an alternate synthesis of the compounds of the present invention wherein A is represented by cyclic guanidines. Alternate reagents and materials known to those skilled in the art can be substituted appropriately as readily recognized by one skilled in the art to produce the desired compounds.

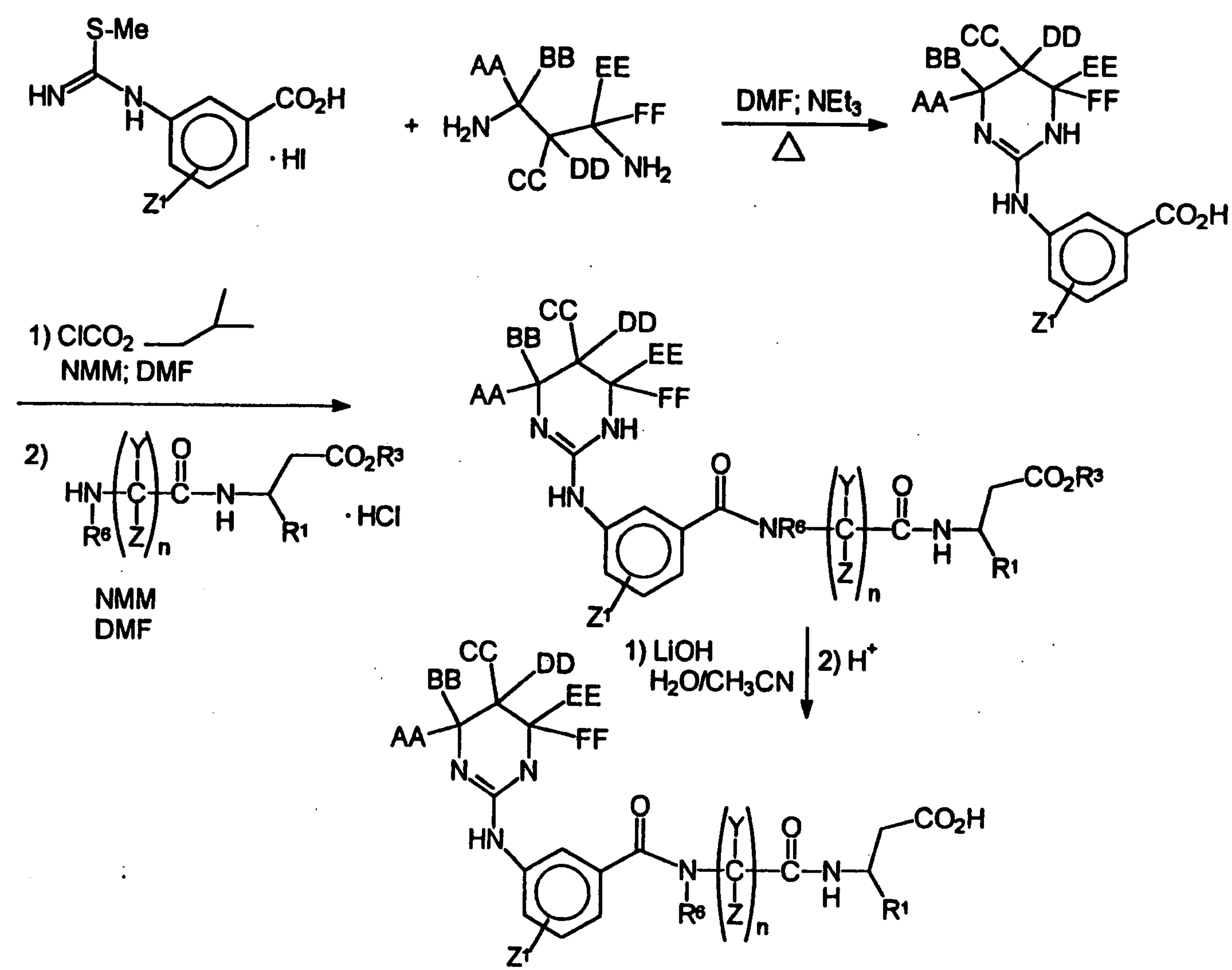
SCHEME XVII

(1)



SCHEME XVII (cont'd)

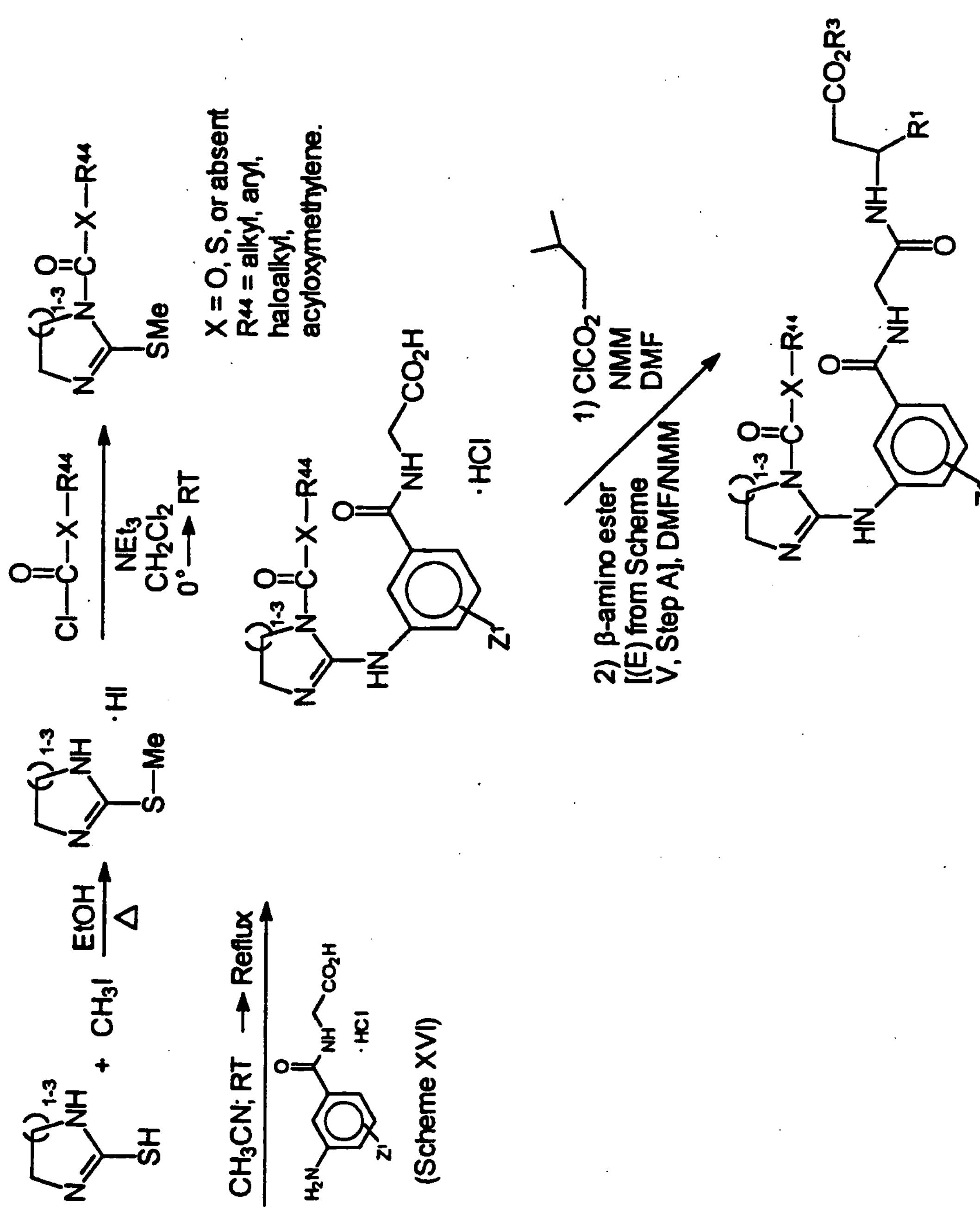
(2)



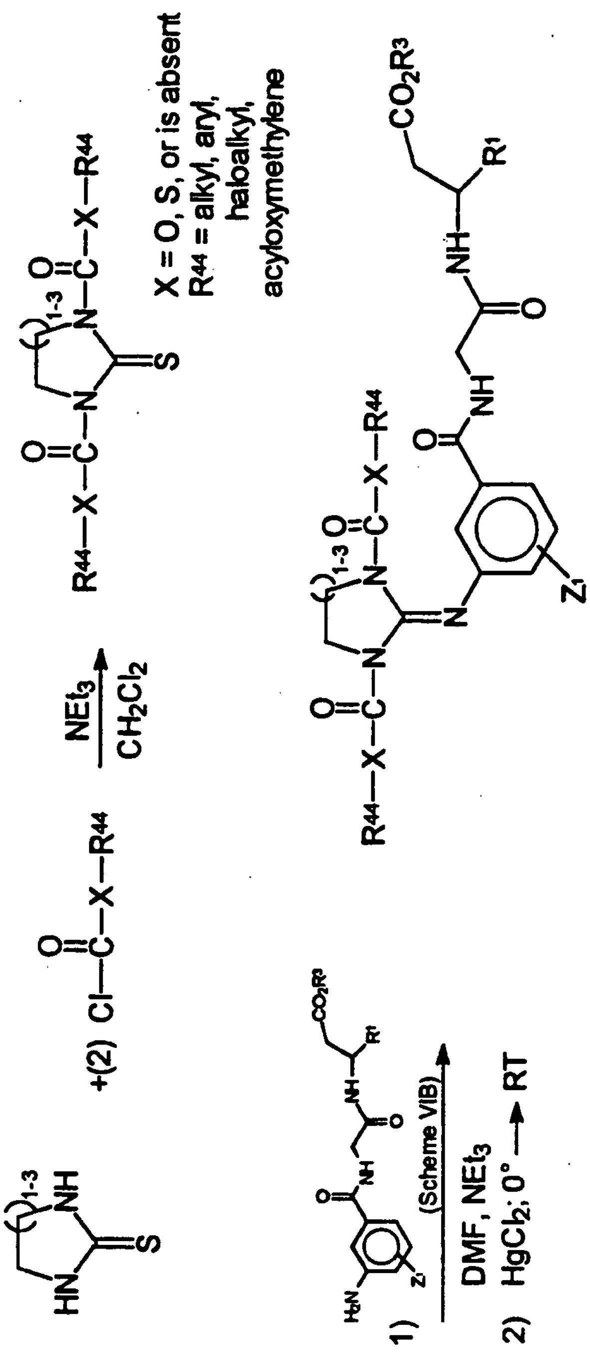
Scheme XVII depicts methods of synthesis wherein A is repr sented by a 5 or 6 membered cyclic guanidine.

AA through FF can be hydrog n or the additional substituents as defined above where A is a dinitrogen heterocycle, provided the appropriate substituted diamine is either commercially available or can be readily synthesized by one skilled in the art.

SCHEME XVIII

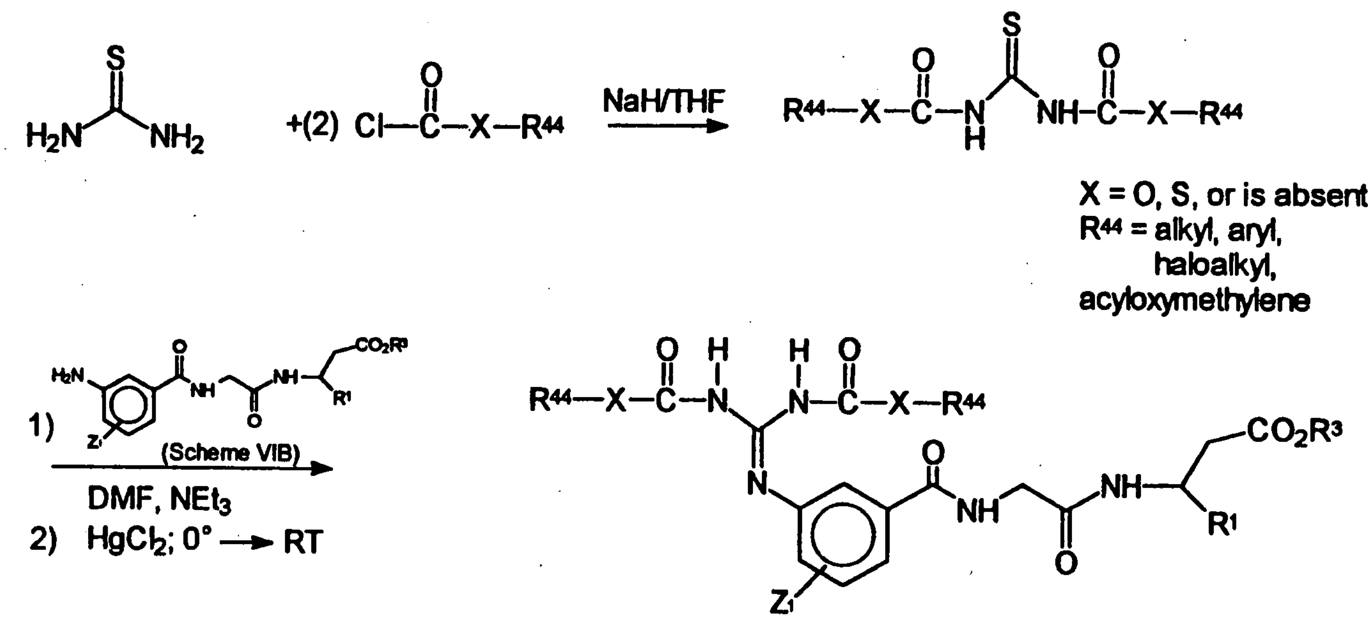


SCHEME XIX


+(2)
NEt3
CH2Cl2
X = O, S, or is absent
R44 = alkyl, aryl, haloalkyl, acyloxymethylene
1) (Scheme VIB)
DMF, NEt3
2) HgCl2; 0° → RT

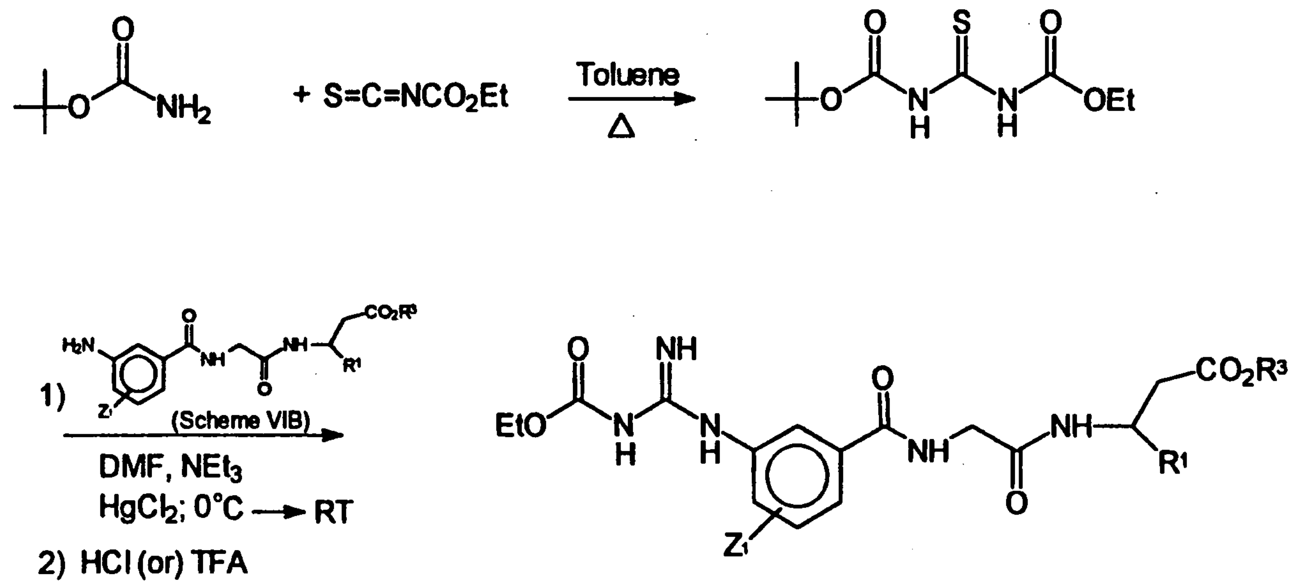
SCHEME XX

A.


NaH/THF
X = O, S, or is absent
R44 = alkyl, aryl, haloalkyl, acyloxymethylene
1)
(Scheme VIB)
DMF, NEt3
2) HgCl2; 0° → RT

SCHEME XX (cont'd)

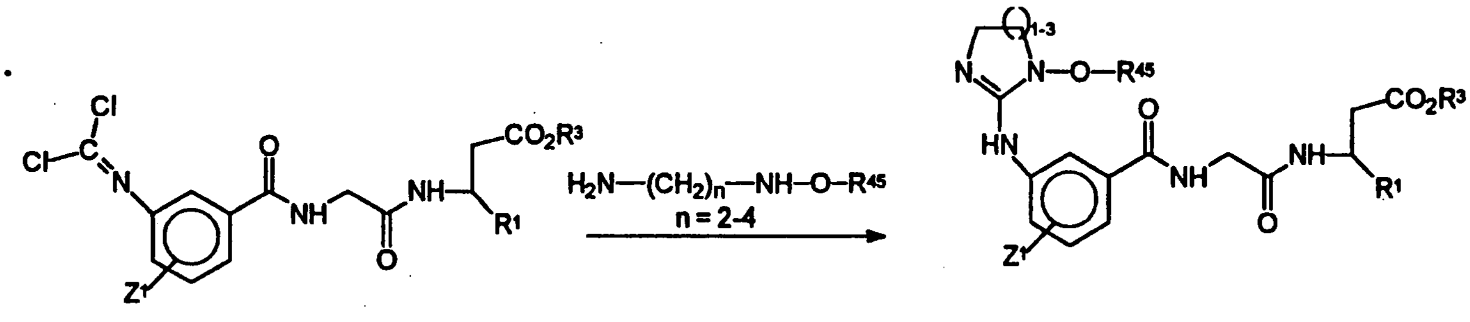
B.



Schemes XVIII-XX represent synthesis of pot ntial pro-drugs where either one or tw of the guanidine nitrogens are derivatiz d with a p tentially labil functionality. These methods are intended to be merely illustrative of methodology for preparing the compounds of the present invention, and not limiting thereof in either scope or spirit. Other methodologies, reagents and conditions known to those skilled in the art may be employed to synthesize the compounds of the present invention.

SCHEME XXI

A.

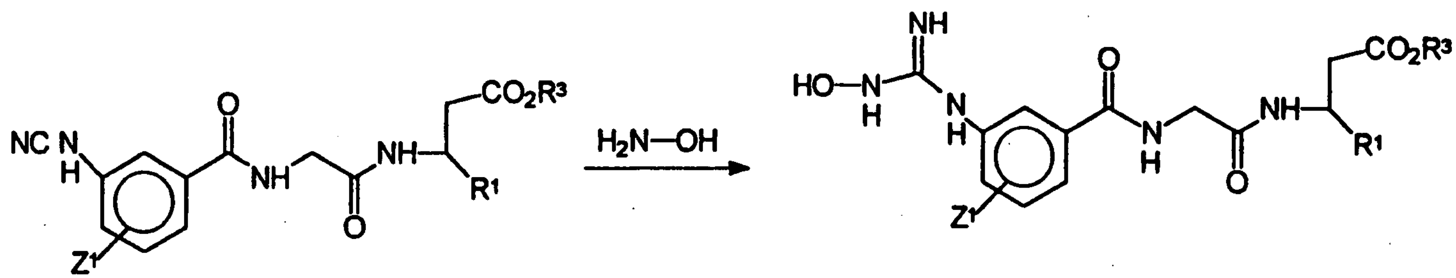


R45 is H, alkyl, aryl or aralkyl

from Scheme VIB
and reference (1)

reference (1) = DE2847766

B.



from Scheme VIB
and reference (2)

reference (2) = Sci. Pharm. (1989), 57(4), 375-80.

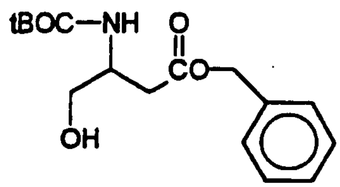
Scheme XXI further illustrat s examples of potential pro-drugs or active entities of compounds of the pr sent inventi n.

In particular, Scheme XXI illustrates the synthesis of N-hydroxy or N-alkoxy analogues of cyclic and acyclic guanidine compounds.

The cited references provide synthetic details of the appropriate derivatization of the anilines exemplified in Scheme VIB.

Example A

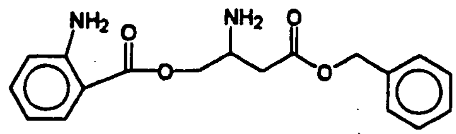
Preparation of benzyl-3-N-t-Boc-amino-4-hydroxy-(3S)-butyrate



N-t-Boc-L-aspartic acid, β-benzyl ester (75 g, 20 mmol) was dissolved in THF (30 ml) and added dropwise over a period of 30 minutes to BH_3-THF (400 ml, 40 mmol) at 0°C under a N_2 atmosphere. After the solution was stirred for 2.5 hours at 0°C, the reaction was quenched with 10% acetic acid in MeOH (50 ml), and the solvent was evaporated. The residue was dissolved in ether (200 ml) and washed with 1N HCl, saturated K_2CO_3, water and dried over $MgSO_4$. The product was isolated by removal of the solvent *in vacuo* (mp 56-57°C from isopropyl ether/hexane). ^{1}H-NMR (d_6-DMSO) δ 1.4 (s, 9H), 2.68 (d, 2H, J=6 Hz), 3.82 (d, 2H, J=5 Hz), 4.01 (m, 1H), 5.16 (s, 2H), 5.21 (bs, 1H), 7.37 (bs, 5H).

Example B

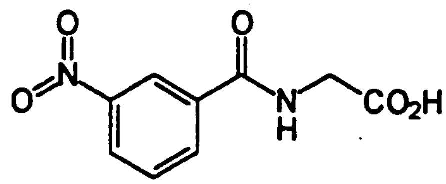
Preparation of benzyl-3-amino-4-(anthranilate)-(3S)-butyrate.



Benzyl-3-N-t-Boc-amino-4-hydroxy-(3S)-butyrate from Example A (10 g, 32 mmol) was dissolved in dimethylformamide (50 ml) followed by triethylamine (4.4 g, 46 mmol). Isatoic anhydride (5.0 g, 3 mmol) was added and the solution was stirred for 24 hours at 25°C. After the reaction (monitored by RPHPLC) was complete, water was added and the product extracted with ethyl acetate (100 mL) and dried over Na_2SO_4. Upon evaporation of solvent 12 g of a yellow oil was obtained. To this oil, was added dioxane (20 mL) followed by 4N HCl in dioxane (20 mL). The reaction was left to proceed for 4 hours, ether was added and an oily mass separated from the solution. Ether was again added to the oily mass and decanted. This procedure was repeated two times. Ether was added to the semi solid and stirred vigorously for 16 hours. A white solid was obtained having MS and NMR consistent with the proposed structure.

Example BB

Preparation of 3-nitrobenzoyl glycine:



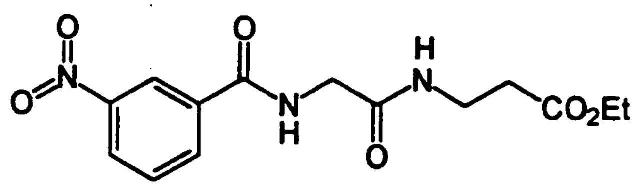
Glycine (20 g, 266 mmol) was added to water (200 mL), followed by potassium hydroxide (20 g, 357 mmol) and cooled to 0°C in an ice bath. To this solution was added 3-nitrobenzoyl chloride (20 g, 108 mmol) in acetonitrile (20 mL) drop-wise over a 10 minute period. After the reaction was complete (3-4 hours) concentrated hydrochloric acid was added until pH = 2 followed by saturated aqueous NaCl (75 mL). The product was filtered, washed with water and air dried (22 g, 90% yield). ^{1}H-NMR (d_6-DMSO) δ, 3.92 (d, 2H, J = 6.1), 7.9 (t, 1H, J = 7.9), 8.3 (t, 1H, J = 5.6), 8.35 (m, 2H), 8.69 (s, 1H), 9.25 (t, 1H, J = 7.2 Hz). MS (FAB) m/e 231.0 (M+Li+).

Elemental Analysis

$C_9H_8N_2O_5$	Calc'd.:	C, 45.89	H, 4.25	N, 9.92
	Found:	C, 45.97	H, 4.44	N, 10.11

Example C

Pr paration of N-[2-[[(3-nitr phenyl)carb nyl]amino]-1-oxoethyl]-β-alanine, ethyl ester



N,N'-Disuccinimidyl carbonate (14 g, 5.5 mmol) was added to 3-nitrobenzoyl glycine (10 g, 4.5 mmol) of Example BB in dry dimethylformamide (30 mL) followed by N,N-dimethylaminopyridine (200 mg). After a period of 1 hour beta-alanine ethyl ester hydrochloride (7 g, 4.6 mmol) in 20% aqueous potassium carbonate (50 mL) was added in one portion. After complete reaction the product was collected by filtration (14 g, 97% yield). ^{1}H-NMR (d_6-DMSO) δ, 1.18 (t, 3H, J = 7.2 Hz), 2.46 (t, 2H, J = 7.0), 3.34 (q, 2H, J_1 = 6.7 Hz, J_2 = 12.6 Hz), 3.87 (d, 2H, J = 5.9 Hz), 4.05 (q, 2H, J_1 = 7.4 Hz, J_2 = 14.2 Hz), 7.8 (t, 1H, J = 8.0 Hz), 8.1 (t, 1H, J = 5.6 Hz), 8.35 (m, 2H), 8.71 (s, 1H), 9.22 (bs, 1H).

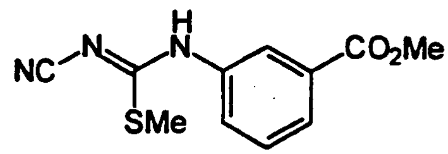
MS (FAB) m/e 324.2 (M+H+).

Elemental Analysis

$C_{14}H_{17}N_3O_6$ H_2O	Calc'd.:	C, 49.26	H, 4.99	N, 12.32
	Found:	C, 49.42	H, 5.01	N, 12.21

Example D

Preparation of methyl 3-[[(cyanoimino)(methylthio)-methyl]amino]benzoate

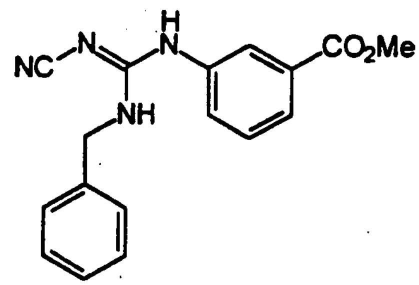


A stirred mixture of 3-aminomethylbenzoate (6.04 g, 40 mM) and dimethyl N-cyanodithioiminocarbonate (11.96 g, 80 mM) in pyridine (70 ml) was heated at reflux under a nitrogen atmosphere for 2.5 hours. The reaction mixture was cooled to room temperature. On standing overnight at room temperature the title compound crystallized from the reaction mixture affording 6.2 g (two crops). The title compound was used without further purification in the proceeding examples.

NMR was consistent with the proposed structure.

Example E

Preparation of methyl 3-[[(cyanoimino)[(phenylmethyl)-amino]methyl]amino]benzoate

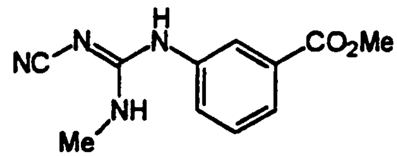


A stirred mixture of the compound from Example D (1.0 g) and benzylamine (440 mg) in ethanol (15 ml) was heated at reflux under a nitrogen atmosphere for 3 hours. The reaction mixture was cooled to room temperature. On standing overnight at room temperature a white solid was obtained and isolated by filtration (720 mg). The crude filtrate was further purified by chromatography on silica (eluant; ethyl acetate/hexane, 1:1) to afford the title compound (550 mg) as a white solid.

NMR was consistent with the proposed structure.

Example F

Preparati n of methyl 3-[[(cyanoimino)(methylamino)-methyl]amino]benzoate

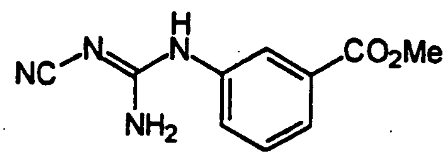


The title compound was prepared as described in Example E, replacing benzylamine with an equivalent amount of methylamine. The title compound was obtained as a white solid (55% yield).

NMR was consistent with the proposed structure.

Example G

Preparation of methyl 3-[[amino(cyanoimino)methyl]-amino]benzoate

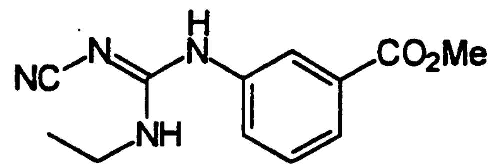


A mixture of the compound from Example D (1.0 g) and ammonium hydroxide (2 ml) in ethanol (20 ml) was heated at 70° in a sealed tube for 3.5 hours. The reaction mixture was cooled to room temperature and reduced to half its volume. After standing overnight at room temperature a white solid was obtained, which was isolated by filtration and washed with methanol. This afforded the title compound (389 mg) as a white solid.

NMR was consistent with the proposed structure.

Example H

Preparation of m thyl 3-[[(cyanoimino)(ethylamino)-methyl]amino]benzoate

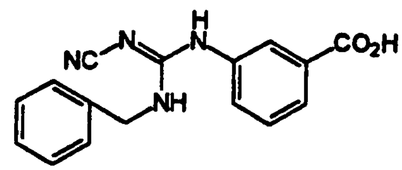


The reaction was carried out as described in Example G except ammonium hydroxide was replaced with an equivalent amount of ethyl amine. This afforded the title compound (78%) as a white solid.

NMR was consistent with the proposed structure.

Example I

Preparation of 3-[[(cyan imino)(phenylmethyl)amin]-methyl]amino]benzoic acid

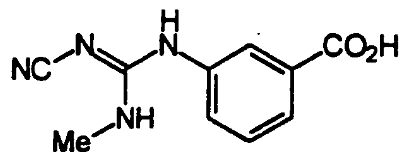


To a stirred solution of the compound from Example E (250 mg) in THF (2 ml) and MeOH (2 ml), 1N-NaOH (2 ml) was added. The reaction mixture was stirred at room temperature for 2 hours and concentrated *in vacuo* to afford a white solid. The residue was acidified by suspension in water followed by addition of 1N-HCl. The resultant solid was filtered, washed with diethyl ether and dried to afford the title compound (140 mg) which was used in subsequent examples without further purification.

NMR was consistent with the proposed structure.

Example J

Preparation f 3-[[(cyanoimino)(m thylamino)methyl]-amino]benzoic acid

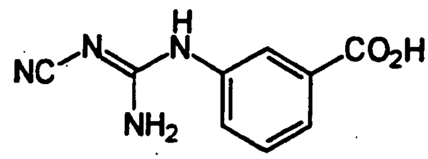


The title compound was prepared as described in Example I except the compound of Example E was replaced with an equivalent amount of the compound of Example F. This afforded the title compound (87%) as a white solid.

NMR was consistent with the proposed structure.

Example K

Preparation of 3-[[amino(cyanoimino)methyl]amino]-benzoic acid

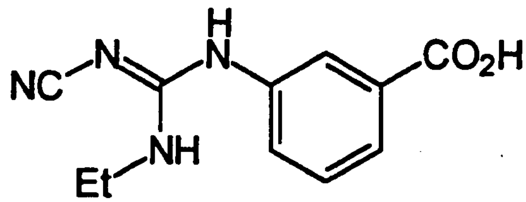


The title compound was prepared as described in Example I except that the compound of Example E was replaced with an equivalent amount of the compound of Example G. This afforded the title compound (92%) as a white solid.

NMR was consistent with the proposed structure.

Example L

Preparation of 3-[[(cyanoimino)(ethylamino)methyl]-amino]benzoic acid

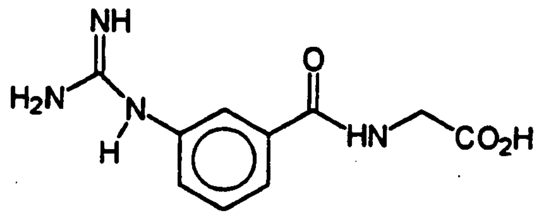


The title compound was prepared as described in Example I except that the compound of Example E was replaced with an equivalent amount of the compound of Example H. This afforded the title compound (81%) as a white solid.

NMR was consistent with the proposed structure.

Example M

Preparation of m-guanidinohippuric acid HCl



Step A

A solution of glycine (200 g) and KOH (200 g) in water (1000 ml) at 0°C was treated dropwise with a solution of m-nitrobenzoyl chloride (100 g) in acetonitrile (100 ml). The reaction was allowed to warm to room temperature and was stirred for 4 hours. 12N aqueous HCl was added until pH <2. The reaction was allowed to stand overnight at room temperature. The resulting solid was filtered and washed with water (2 x 250 ml) and dried *in vacuo* at 60°C. 100 g of m-nitrohippuric acid was isolated. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Step B

A suspension of m-nitrohippuric acid (50 g) and 5% Pd/C (5 g) in methanol (200 ml) was subjected to 50 psi of H_2. After 2 hours, the reaction was filtered. The resulting gray solid was washed with 2% aqueous HCl (2 x 250 ml). The yellowish solution was lyophilized to give m-aminohippuric acid HCl (30 g).

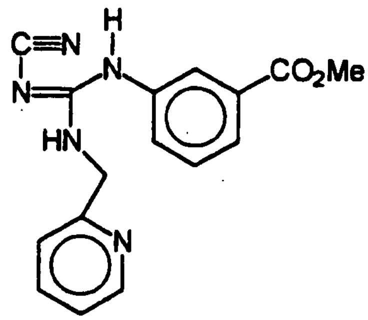
Step C

A mixture of m-aminohippuric acid HCl (10 g), NMM (12 ml) and 1H-pyrazole-1-carboxamidine HCl (8.3 g) in dioxane (80 ml) and water (20 ml) was refluxed for 6 hours. The heat was removed and the reaction cooled to room temperatur . Saturated aque us NaCl (10 ml) was added and the reaction mixture was filtered. The resulting solid was washed with dioxane (20 ml)

followed by acetone (20 ml). The salm n color solid was dissolved in 1:1 $CH_3CN:H_2O$ and treated with 20% aqueous HCl (pH <3). Th lyophilized solid, m-guanidinohippuric acid HCl (10 g), had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Example N

Preparation of methyl 3-[[(cyanoimin)[(2-pyridinylmethyl)amino]methyl]amino]benzoate

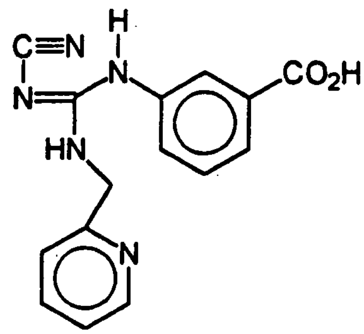


The title compound was prepared following the procedure described in Example E, replacing benzyl amine with an equivalent amount of 2-(aminomethyl)-pyridine. The title compound was obtained as a white solid (75% yield).

NMR was consistent with proposed structure.

Example O

Preparation f 3-[[(cyanoimino)[(2-pyridinylmethyl)-amino]methyl]amino]benzoic acid

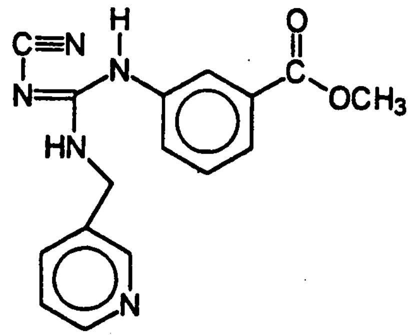


The title compound was prepared following the procedure described in Example I except that the compound of Example E was replaced with an equivalent amount of the compound of Example N. This afforded the title compound as a white solid (70% yield).

NMR was consistent with the proposed structure.

Example P

Preparation of methyl 3-[[(cyanoimino)[(3-pyridinylmethyl)amino]methyl]amino]benzoate

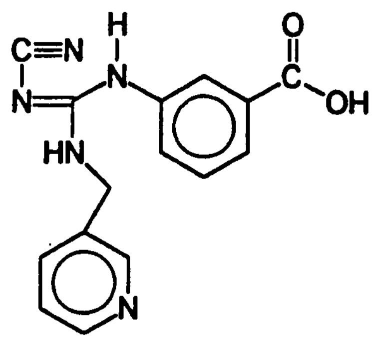


The title compound was prepared following the procedure described in Example E, replacing benzyl amine with an equivalent amount of 3-(aminomethyl)-pyridine. The title compound was obtained as a white solid (70% yield).

NMR was consistent with the proposed structure.

Example Q

Preparation of 3-[[(cyanoimino)[(3-pyridinylmethyl)-amino]methyl]amino]benzoic acid

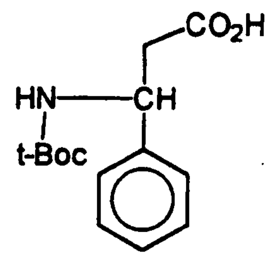


The title compound was prepared following the procedure described in Example I except that the compound of Example E was replaced with an equivalent amount of the compound of Example P. This afforded the title compound as a white solid (65% yield).

NMR was consistent with the proposed structure.

EXAMPLE R

Preparation of

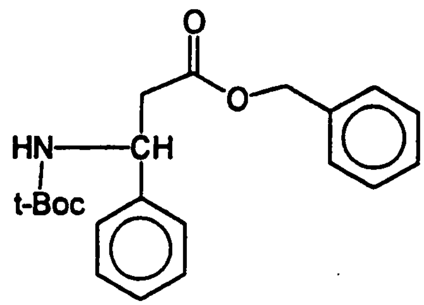


To a stirred solution of DL-3-amino-3-phenyl propionic acid (16.5 g, 0.1 M), dioxane (160 ml), water (40 ml), and triethylamine (25 ml) were added di-tert-butyl dicarbonate (18.6 g, 0.1 mole). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated NaCl and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product (8.9 g), which was taken up in the next step (Example S) without further purification.

NMR was consistent with the proposed structure.

EXAMPLE S

Preparation of

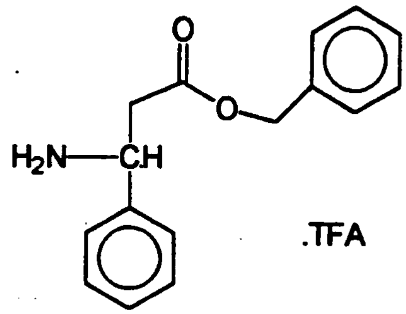


To a stirred solution of the compound from Example R (8.3 g, 30 mmole) in DMF (50 ml), K_2CO_3 (10 g) and benzyl bromide (5.7 g, 30 mmole) were added. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 16 hours. The reaction mixture was diluted with water (400 ml) and extracted with ethyl acetate. The organic layer was separated and washed with water, 5% $NaHCO_3$, water, dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude ester (8.5 g). The title compound was used in the next step (Example T) without further purification.

NMR was consistent with the proposed structure.

EXAMPLE T

Preparation of



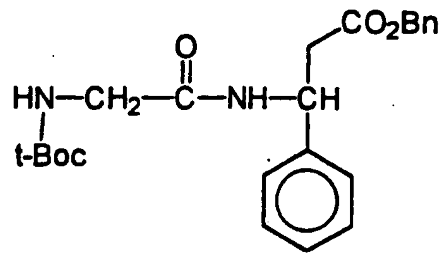
.TFA

To a stirred solution of the compound from Example S (2.0 g) in methylene chloride (20 ml), trifluoroacetic acid (20 ml) was added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* to afford 2.05 g of crude product, which was taken up in the next step (Example U) without further purification.

NMR was consistent with the proposed structure.

EXAMPLE U

Preparation of

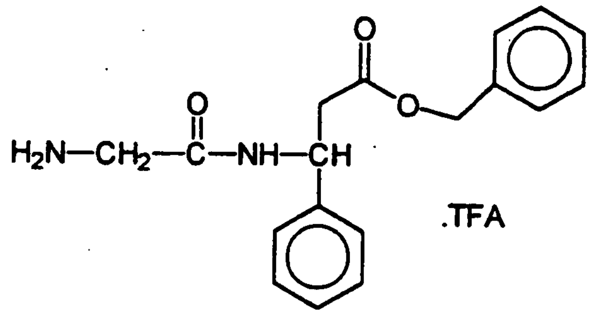


A stirred solution of N-t-Boc-Glycine (876 mg, 5 mmole), methylene chloride (20 ml), N-methylmorpholine (1.01 g) at 0°C, IBCF (690 mg) was added and the reaction mixture was stirred at 0°C for 15 minutes. The product of Example T (1.845 g) was added to the reaction mixture at 0°C. The reaction mixture was warmed to room temperature and was stirred for a further 6 hours. The mixture was washed with water, followed by saturated sodium bicarbonate solution and water, dried (Na_2SO_4), and concentrated *in vacuo* to afford crude product (2.2 g). The crude product was purified through a flash column using 92.5:7:0.5/$CHCl_3$:ethanol:NH_4OH as eluent to give the title compound (1.82 g) as an oil.

NMR spectrum was consistent with the proposed structure.

EXAMPLE V

Preparation of

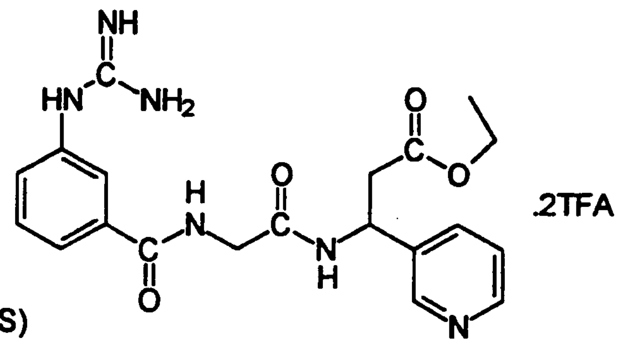


To a stirred solution of the product of Example U (1.8 g) and methylene chloride (20 ml) was added trifluoroacetic acid (12 ml), and the reaction mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* to afford crude product (1.7 g) as an oily gum, which was used in the next step (Example 132, Example 133, Example 134) without further purification.

NMR was consistent with the proposed structure.

Example 1

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To 3-pyridine carboxaldehyde (300 ml) in 2-propanol (3 liters) was added ammonium acetate (297 g) followed by malonic acid (398 g). The reaction mixture was stirred at reflux for 5 hours. The precipitate was filtered while hot and washed with hot isopropanol (2 liters). The resulting white solid was then dried to yield DL-3-amino-3-(3-pyridyl)propionic acid (220 g) as a white solid.

NMR and MS were consistent with the desired product.

Step B

DL-3-amino-3-(3-pyridyl)propionic acid (220 g) from Step A was slurried in absolute EtOH (3.6 liters). HCl gas (one lecture bottle - ½ lb) was bubbled into the reaction while stirring over 40 minutes (slow exotherm to 61°C). The slurry was then heated at reflux for 4 hours (a solution forms after 1 to 1.5 hours). The reaction mixture was cooled to 5°C in an ice bath. After stirring at 5°C for 1.5 hours, the resulting white precipitate was filtered and washed thoroughly with ether. After drying under vacuum at 50°C, the yield of ethyl DL-3-amino-3-(3-

pyridyl)propionate dihydrochloride was 331.3 g as a white solid.

NMR and MS were consist nt with th desired product.

Step C

To ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride (220.6 g, 0.83 mole) from Step B in anhydrous THF (2 liters) and triethylamine (167.2 g, 1.65 moles), N-t-BOC-glycine N-hydroxysuccinimide ester (225 g, 0.826 moles)(Sigma) was added in several portions at 5-10°C (no exotherm). The reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered and washed with THF. The solvent from the filtrate was then removed under vacuum. The residue was taken up in ethyl acetate (2.3 liters). The ethyl acetate layer was washed with saturated sodium bicarbonate (2 x 900 ml) and H_2O (3 x 900 ml), dried over $MgSO_4$ and removed under vacuum. The residue was slurried overnight in 10% ethyl acetate/hexane (2.5 liters). The precipitate was filtered, washed with 10% ethyl acetate/hexane (1 liter), then hexane, then dried to yield ethyl β-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]acetyl]amino]-pyridine-3-propanoate (233 g) as a white solid.

NMR and MS were consistent with the desired structure.

Step D

Ethyl β-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-acetyl]amino]pyridine-3-propanoate (from Step C) (232 g, 0.66 mole) was dissolved in warm dioxane (1 liter). After cooling to room temperature, 4M HCl in dioxane (1.6 liters) (Aldrich) was slowly added. A white precipitate formed aft r several minutes and then turned to a thick goo. After 2 hours, the s lvent was decanted off. The goo was slurri d in ther and the

ether decanted off until a white solid resulted. This was dried under vacuum to yield ethyl β-[(2-aminoacetyl)amino]pyridine-3-propan ate, bis hydrochloride salt (224.2 g) as a white hygroscopic solid.

NMR and MS were consistent with the desired structure.

Step E

To 3,5-dimethylpyrazole-1-carboxamidine nitrate (6 g, 0.03 mole) (Aldrich) and diisopropylamine (3.8 g, 0.03 mole) in dioxane (20 ml) and H_2O (10 ml) was added 3-aminobenzoic acid (2.7 g, 0.02 mole). The reaction was stirred at reflux for 2.5 hours then overnight at room temperature. The resulting precipitate was filtered, washed with dioxane/H_2O and dried. The precipitate was then slurried in H_2O and acidified with concentrated HCl until a solution formed. The solvent was removed under vacuum and the residue was slurried twice in ether (ether decanted off). The product was dried under vacuum to yield 3-guanidinobenzoic acid hydrochloride (1.77 g) as a white solid. MS and NMR were consistent with the desired structure.

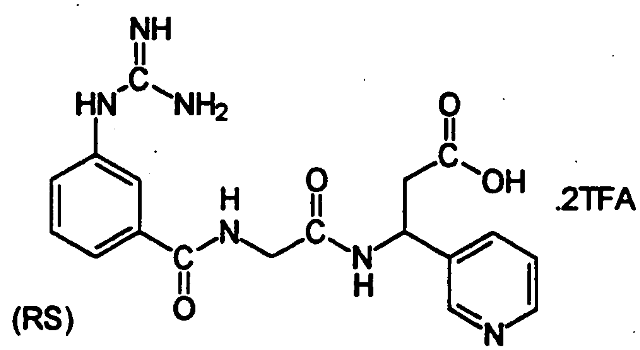
Step F

To the product from Step E (0.49 g, 0.0023 mole) and N-methylmorpholine (0.23 g, 0.0023 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (0.31 g, 0.0023 mole) at ice bath temperature. After stirring for 5 minutes at ice bath temperature, a slurry of the product from Step D (0.73 g, 0.0023 mole) and N-methylmorpholine (0.46 g, 0.0045 mole) in anhydrous DMF (8 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath and the product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[3-[(aminoimin methyl)-

amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-pr panoate, bis(trifluoroacetate) salt (800 mg) as a hygroscopic white s lid. MS and NMR were consistent with the desired structure.

Example 2

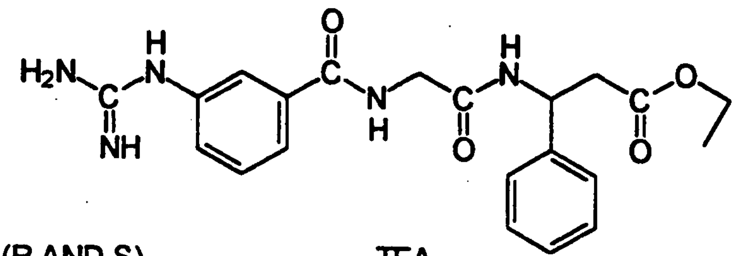
Preparation of (±)β-[[2-[[[3-[(aminoiminom thyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product from Example 1 (700 mg, 0.001 mole), in H_2O (20 ml) was added LiOH (160 mg, 0.0038 mole). The reaction mixture was stirred for 1 hour at room temperature. After lowering the pH to ≈5 with TFA, the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (640 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 3

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoate, trifluoroacetate salt



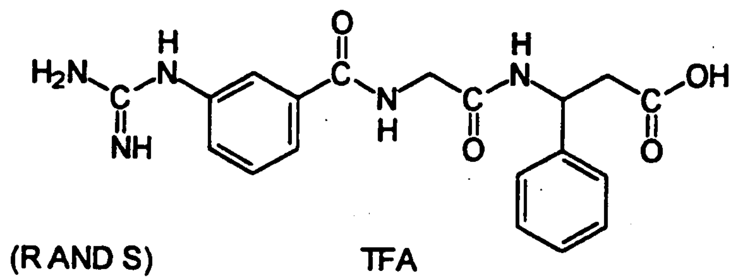
(R AND S) TFA

The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Step A.

NMR and MS were consistent with the desired structure.

Example 4

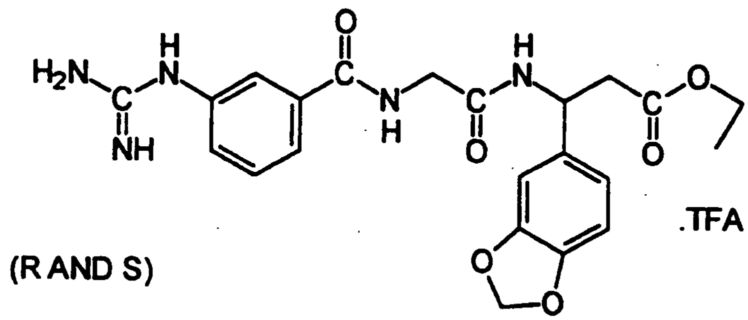
Preparation of (±)β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]benzene-propanoic acid, trifluoroacetate salt



To the product of Example 3 (0.37 g, 0.0007 mole) in H_2O (10 ml) was added LiOH (80 mg, 0.002 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ≈3 with TFA and the product was isolated by RPHPLC to yield β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt (280 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 5

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoate, trifluoroacetate salt

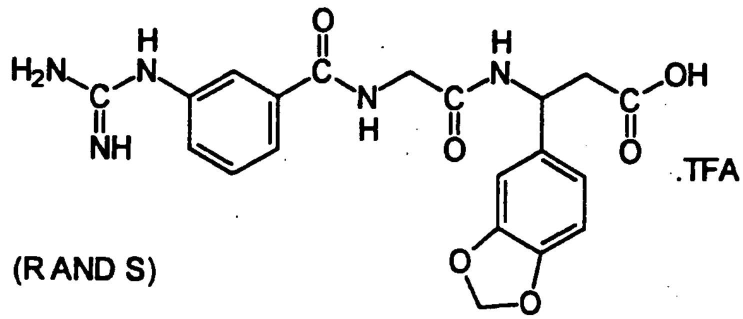


The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of piperonal (Aldrich) for 3-pyridinecarboxaldehyde in Step A.

MS and NMR were consistent with the desired structure.

Example 6

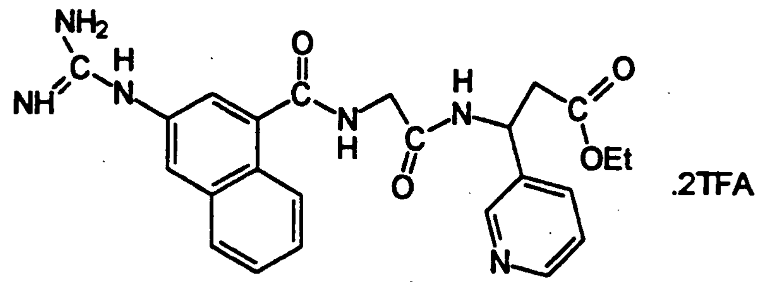
Preparation f (±)β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, trifluoroacetate salt



To the product of Example 5 (0.35 g, 0.0006 mole) in H_2O (40 ml) and CH_3CN (5 ml) was added LiOH (70 mg, 0.0017 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ≈4.5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, trifluoroacetate salt (280 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 7

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]naphthalen-1-yl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate)salt



(RACEMIC)

Step A

To methyl 3-nitro-1-naphthoate (2.5 g, 0.011 mole)(Aldrich) in MeOH/H_2O (40 ml)(1:1) was added LiOH (1.8 g, 4 equivalents). The solution was stirred overnight at room temperature. The solvent was removed under a stream of N_2. The residue was dissolved in H_2O and the solution acidified with concentrated HCl. The resulting precipitate was filtered, washed with H_2O and dried to yield 3-nitro-1-naphthoic acid (2.18 g) as a white solid.

Step B

3-Nitro-1-naphthoic acid (1.77 g, 0.008 mole) was dissolved in a minimum of warm MeOH. 10% Pd/C (300 mg) was added and the reaction shaken on a Parr shaker under 50 psi H_2 for 5 hours. The catalyst was filtered through celite and the solvent was removed under vacuum. The residue was dried to yield 3-amino-1-naphthoic acid (1.43 g) as a pink colored solid.

Step C

To 3,5-dimethylpyrazol -1-carb xamidine nitrate (1.6 g, 0.008 mole)(Aldrich) and diisopropylethylamine (1.02 g, 0.008 mole) in dioxane (5 ml) and H_2O (2.5 ml) was added 3-amino-1-naphthoic acid (1 g, 0.0053 mole). The reaction mixture was stirred at reflux overnight. The reaction was cooled to room temperature and the precipitate was filtered, washed with dioxane/H_2O then dried. The precipitate was then slurried in H_2O and acidified with concentrated HCl. The solvent was removed under vacuum on a 70°C water bath. The residue was slurried in ether 3 x (ether decanted off), then dried under vacuum to yield 3-guanidino-1-naphthoic acid hydrochloride (460 mg) as a white solid.

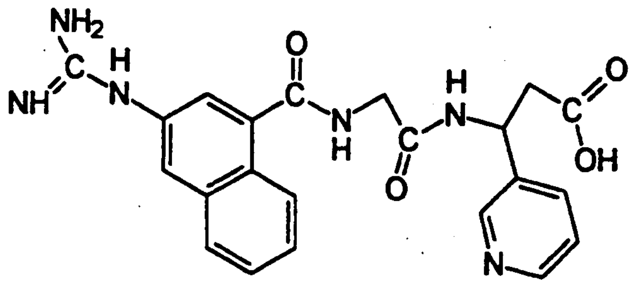
Step D

To 3-guanidino-1-naphthoic acid hydrochloride (400 mg, 0.0015 mole) and N-methylmorpholine (150 mg) in anhydrous DMF (8 ml) was added isobutylchloroformate (210 mg) at ice bath temperature. After stirring at ice bath temperature for 5 minutes, a slurry of the product from Example 1, Step D (490 mg, 0.0015 mole), N-methylmorpholine (300 mg) and anhydrous DMF (6 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath. The product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[1-[(aminoiminomethyl)amino]naphthalen-3-yl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate)salt (410 mg) as a white solid.

NMR and MS were consistent with the desired structure.

Example 8

Preparation of (±)β-[[2-[[[3-[(aminoimin methyl)-amino]naphthalen-1-yl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt



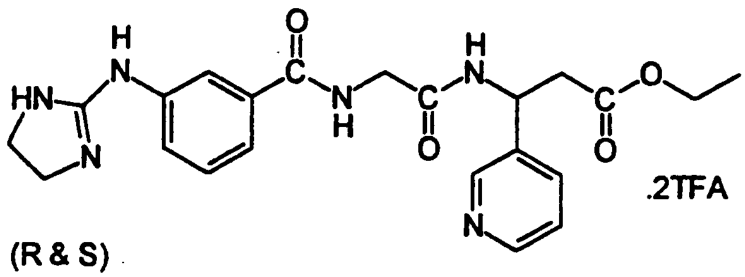
.2TFA

(RACEMIC)

To the product of Example 7, Step D (280 mg, 0.0004 mole) in H_2O (15 ml) and CH_3CN (2 ml) was added (70 mg, 0.0016 mole) LiOH. The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[1-[(aminoiminomethyl)-amino]naphthalen-3-yl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (240 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 9

Preparation of (±)ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To 2-methylthio-2-imidazoline hydroiodide (14.6 g, 0.06 mole)(Aldrich) and diisopropylethylamine (7.6 g, 0.06 mole) in dioxane (40 ml) and H_2O (20 ml) was added 3-aminobenzoic acid (5.4 g, 0.04 mole). The reaction was stirred overnight at reflux. The solution was cooled in an ice bath and the resulting precipitate was filtered and washed with dioxane. The crude product was purified by RPHPLC to yield 3-(2-aminoimidazoline)-benzoic acid (800 mg).

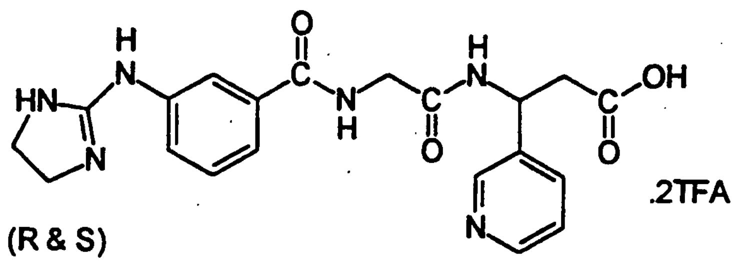
Step B

To the product from Step A (400 mg, 0.00125 mole) and N-methylmorpholine (130 mg, 0.00125 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (170 mg, 0.00125 mole). After stirring at ice bath temperature for 5 minutes, the product from Example 1, Step D (410 mg, 0.00125 mole) and N-methylmorpholine (250 mg, 0.0025 mole) in anhydrous DMF (6 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 79°C water bath and the product was isolated by RPHPLC to yield (±)ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoate,

bis(trifluoroacetate) salt (600 mg) as a hygroscopic whit s lid. MS and NMR were c nsistent with th desired structure.

Example 10

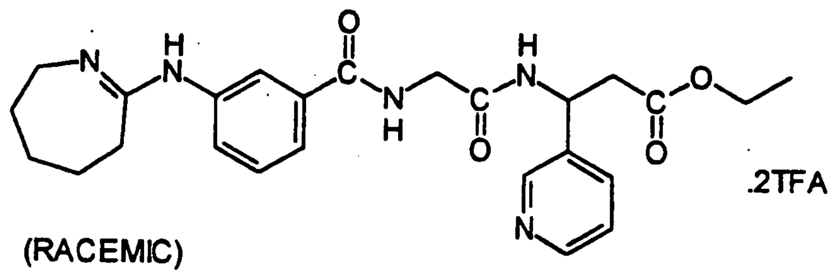
Preparation of (±)β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 9, Step B (450 mg, 0.00068 mole) in H_2O (20 ml) was added LiOH (110 mg, 0.0027 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±)β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt (250 mg) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

Example 11

Preparation of (±) ethyl β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To 1-aza-2-methoxy-1-cycloheptene (3.67 g, 0.0288 mole)(Aldrich) in absolute ethanol (20 ml) was added 3-aminobenzoic acid hydrochloride (5 g, 0.0288 mole). A solution quickly formed. The reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered, washed with ether and dried under vacuum to yield 3-(1-aza-2-amino-1-cycloheptene)-benzoic acid (4.9 g).

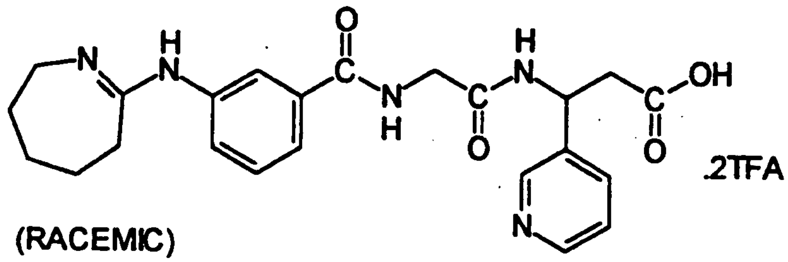
Step B

To the product from Step A (0.5 g, 0.0019 mole) and N-methylmorpholine (0.19 g, 0.0019 mole) in anhydrous DMF (8 ml) was added isobutylchloroformate (0.25 g, 0.0019 mole) at ice bath temperature. After stirring at ice bath temperature for 5 minutes, a slurry of the product from Example 1, Step D (0.6 g, 0.0019 mole) and N-methylmorpholine (0.38 g, 0.0037 mole) in anhydrous DMF (7 ml) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath and the pr duct was isolated by RPHPLC

to yield the title compound (490 mg). NMR and MS were consistent with the desired structure.

Example 12

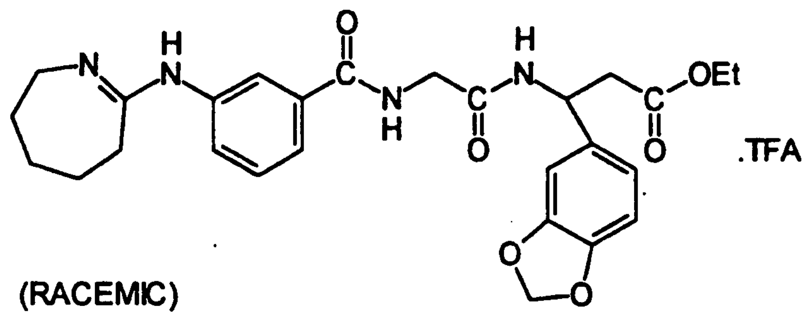
Preparation of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 11, Step B (400 mg, 0.00058 mole) in H_2O (20 ml) was added LiOH (80 mg, 0.0019 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to 4.5 with TFA and the product was isolated by RPHPLC to yield 320 mg of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt as a white solid. MS and NMR are consistent with the desired structure.

Example 13

Preparation of (±)ethyl β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]-1,3-benzodioxole-5-propanoate, TFA salt

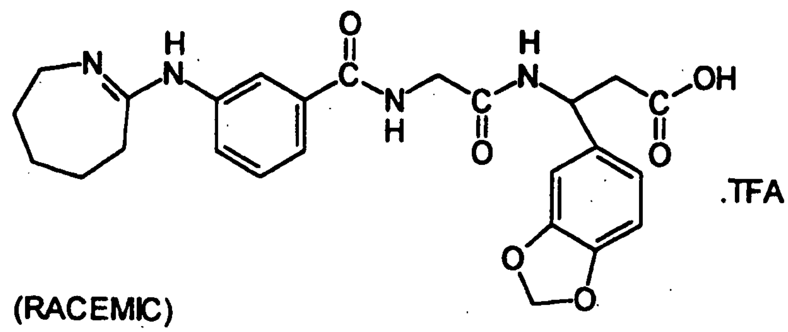


The above compound was prepared according to the methodology of Example 11, substituting the equivalent amount of piperonal (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A, in Example 11, Step B.

MS and NMR were consistent with the desired structure.

Example 14

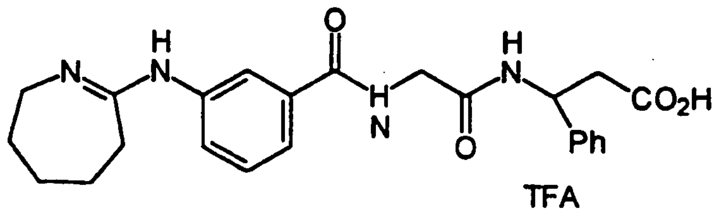
Pr paration of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid, TFA salt



To the product of Example 13 (0.46 g, 0.00091 mole) in H_2O (10 ml) and dioxane (7.5 ml) was added LiOH (80 mg, 0.0018 mole). The reaction was stirred at room temperature for 2 hours. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid (440 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 15

Preparation of (±)β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt

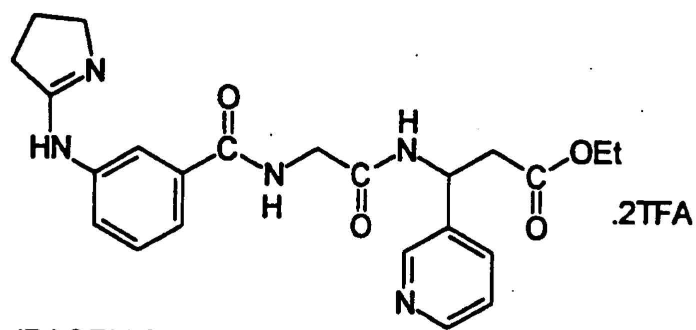


The above compound was prepared according to the methodology of Example 12, substituting the equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Example 1, Step A, and further used in Example 1, Step D as described in Example 11, Step B.

MS and NMR were consistent with the desired structure.

Example 16

Preparation of (±) ethyl β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate) salt



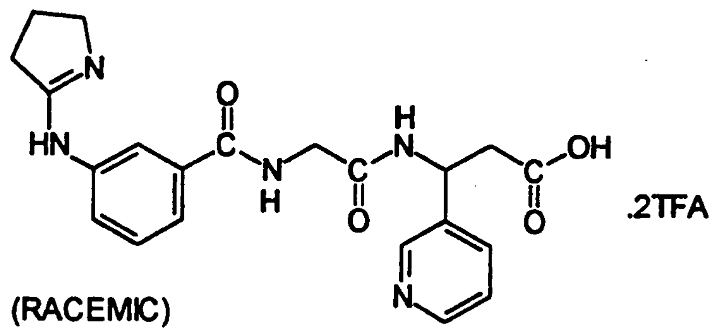
(RACEMIC)

The above compound was prepared according to the methodology of Example 11, substituting 1-aza-2-methoxy-1-cyclopentene* for 1-aza-2-methoxy-1-cycloheptene in Step A. MS and NMR were consistent with the desired structure.

* 1-aza-2-methoxy-1-cyclopentene was made as follows: To 2-pyrrolidinone (2.7 g, 0.033 mole) in CH_2Cl_2 (100 ml) was added trimethyloxonium tetrafluoroborate (10 g)(Aldrich). The reaction was stirred at room temperature for 2 days. Saturated $NaHCO_3$ was added and after shaking in a separatory funnel, the CH_2Cl_2 was separated and distilled off. 1 g of desired product was isolated by further distillation at atmospheric pressure collecting the portion boiling at ≈120°C.

Example 17

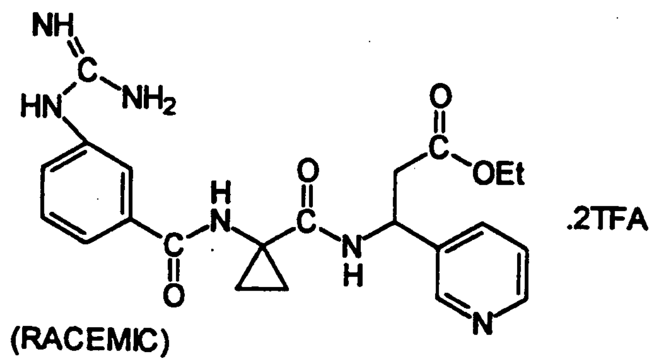
Preparation of β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 16 (380 mg, 0.00057 mole) in H_2O (15 ml) was added LiOH (100 mg, 0.002 mole). The reaction was stirred at room temperature for 2 hours. The pH was lowered to 5 with TFA and the product was isolated by RPHPLC to yield β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (150 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 18

Preparation of (±) ethyl β-[[1-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-1-cyclopropyl]carbonyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt

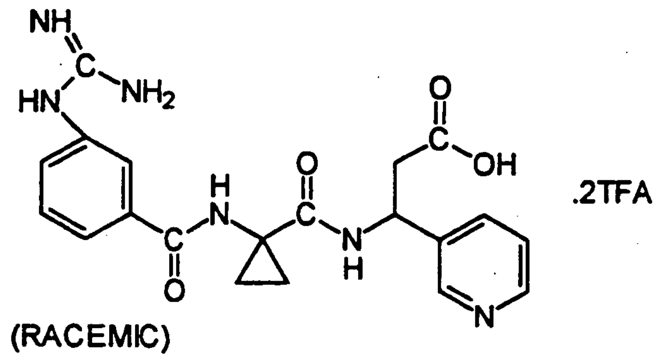


The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of 1-(N-t-Boc-amino)cyclopropane-N-hydroxysuccinimide carboxylate (Sigma) for N-t-BOC-glycine N-hydroxysuccinimide ester in Example 1, Step C.

MS and NMR were consistent with the desired structure.

Example 19

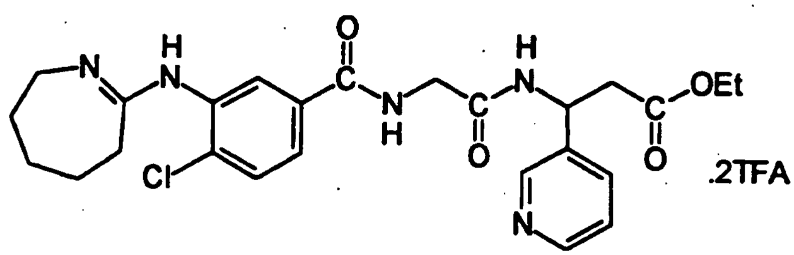
Preparation of β-[[1-[[[3-[(aminoiminom thyl)amino]-phenyl]carbonyl]amino]cycloprop-1-yl]carbonyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 18 (220 mg, 0.00033 mole) in H_2O (15 ml) was added LiOH (60 mg, 0.0013 mole). The reaction was stirred at room temperature for 1.5 hours. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield β-[[1-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-cycloprop-1-yl]carbonyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (170 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 20

Preparation of (±)ethyl β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoate, bis TFA salt

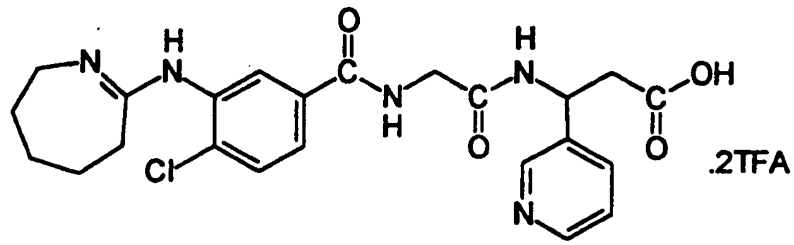


(RACEMIC)

The above compound was prepared according to the methodology of Example 11, substituting an equivalent amount of 3-amino-4-chloro-benzoic acid hydrochloride (Aldrich) for 3-amino-benzoic acid hydrochloride in Example 11, Step A. MS and NMR were consistent with the desired structure.

Example 21

Preparation of (±) β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, bis TFA Salt

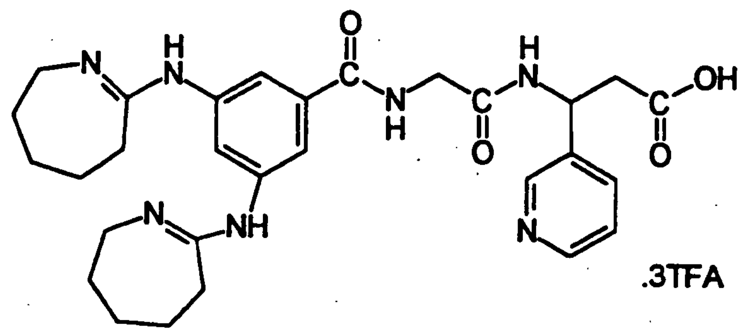


(RACEMIC)

To the product of Example 20 (150 mg, 0.0002 mole) in H_2O (15 ml) was added LiOH (40 mg, 0.0008 mole). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[4-chloro-3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid (100 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 22

Pr paration of (±) β-[[2-[[[3,5-bis[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, tris(trifluoroacetate) salt

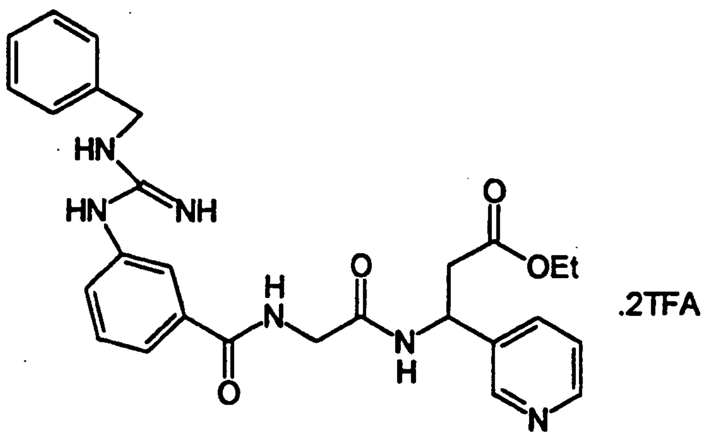


(RACEMIC)

The above compound was prepared according to the methodology of Example 12, substituting an equivalent amount of 3,5-diaminobenzoic acid dihydrochloride (0.3 equivalents) (Fluka) for 3-aminobenzoic acid hydrochloride in Example 11, Step A. MS and NMR were consistent with the desired structure.

Example 23

Preparation of (±) ethyl β-[[2-[[[3-[[imino-[(phenylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

1-(3-Carboxyphenyl)-2-thiourea (5 g, 0.025 mole)(Trans World Chemicals) in THF (75 ml) and CH_3I (3.62 g, 0.025 mole) were stirred at reflux for 2 hours. The solvent was removed under vacuum and the residue was slurried in ether (3X), (the ether decanted off each time) to yield, after drying under vacuum, N-(3-carboxyphenyl)-S-methylisothiouronium hydroiodide (7.8 g) as a yellow solid.

Step B

To the product of Step A (1.5 g, 0.0044 mole) and diisopropylethylamine (0.57 g, 0.0044 mole) in H_2O (5 ml) and dioxane (5 ml) was added benzylamine (0.48 g, 0.0044 mole). The reaction mixture was heated at reflux for 6 hours. The reaction was cooled to room temperature and a precipitate formed. Dioxane (6 ml) was added and the slurry was stirred overnight at room temperature. The precipitate was filtered, washed with dioxane/H_2O, dried, slurried in H_2O, and acidified with concentrated HCl. The solvent was removed under vacuum

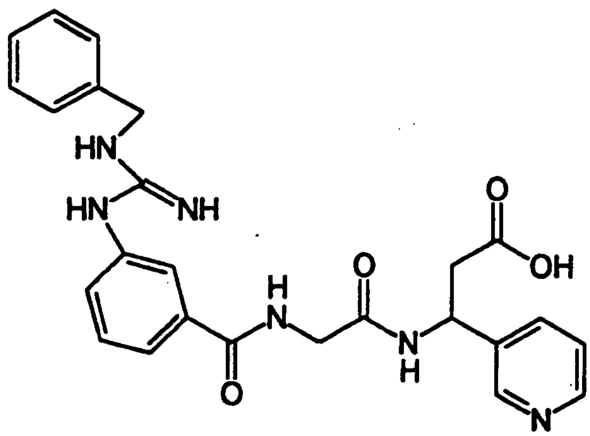
and th residue was slurried in ether (3X; ether d canted off each time). After drying, 1-(3-carboxyphenyl)-2-benzylguanidine hydrochloride (800 mg) was isolated as a white solid. MS and NMR were consistent with the desired structure.

Step C

The title compound was prepared according to Example 1, Step F, substituting an equivalent amount of the product from Step B above for the product from Example 1, Step E in Step F. MS and NMR were consistent with the desired structure.

Example 24

Preparation of (±) β-[[2-[[[3-[[imino[(phenylmethyl)-amino]methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt

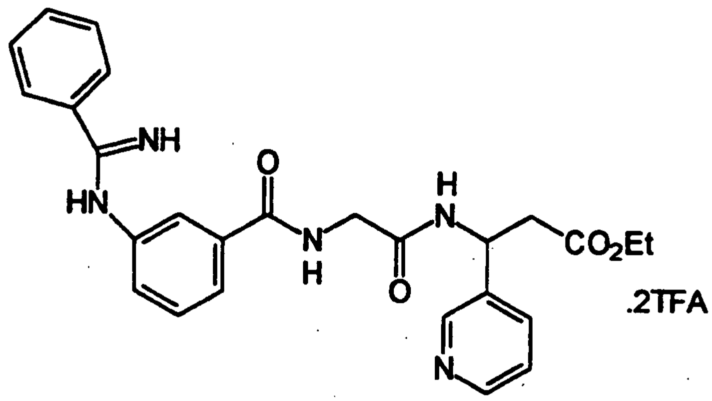


.2TFA

To the product of Example 23, Step C (330 mg, 0.00045 mole) in H_2O (20 ml) was added LiOH (80 mg). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[[imino[(phenylmethyl)amino]methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (330 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 25

Preparation of (±) ethyl β-[[2-[[[3-[(iminophenylmethyl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

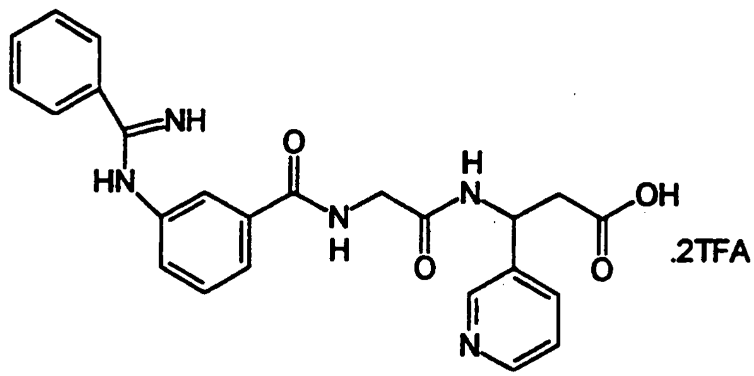
To ethyl benzimidate hydrochloride (3 g, 0.016 mole)(Fluka) and (2.1 g, 0.016 mole) diisopropylethylamine in H_2O (15 ml) and dioxane (15 ml) was added 3-aminobenzoic acid (2.22 g, 0.016 mole) (Aldrich). The reaction mixture was stirred at room temperature for 4 days. The resulting precipitate was filtered, washed with dioxane/H_2O and dried. The precipitate was slurried in H_2O and acidified with concentrated HCl. The solvent was removed under vacuum and the residue was slurried in ether. The ether was decanted off and the residue dried under vacuum to yield N-(3-carboxyphenyl)benzamidine hydrochloride (700 mg) as a white solid. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 1, Step F, substituting an equivalent amount of the product from Step A above for the product from Example 1, Step E in Step F. MS and NMR were consistent with the desired structure.

Example 26

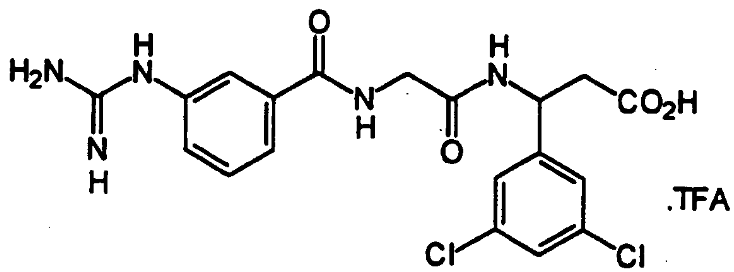
Preparation of (±) β-[[2-[[[3-[(iminophenylmethyl]-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



To the product of Example 25, Step B (240 mg, 0.0034 mole) in H_2O (20 ml) was added LiOH (50 mg). The reaction mixture was stirred at room temperature for 35 minutes. The pH was lowered to 3 with TFA and the product was isolated by RPHPLC to yield (±) β-[[2-[[[3-[(iminophenylmethyl]amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt (120 mg) as a white solid. MS and NMR were consistent with the desired structure.

Example 27

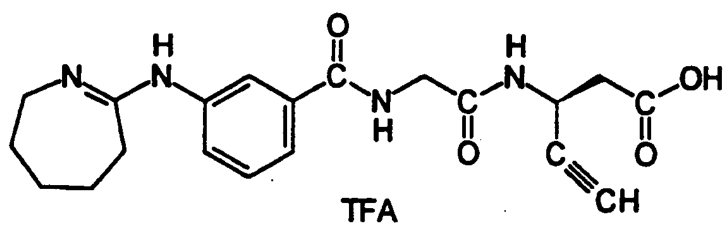
Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt



The above compound was prepared according to the method of Example 2 substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A.

Example 30

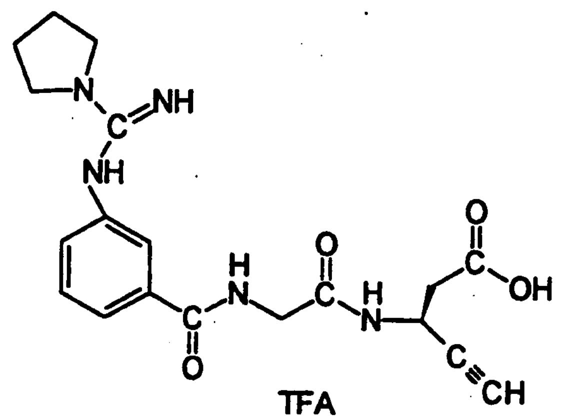
Preparati n of βS-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to the method of Example 12, substituting an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride (J. Med. Chem. 1995, 38, 3378-2394) for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and further used in Example 1, Step D as described in Example 11, Step B.

Example 34

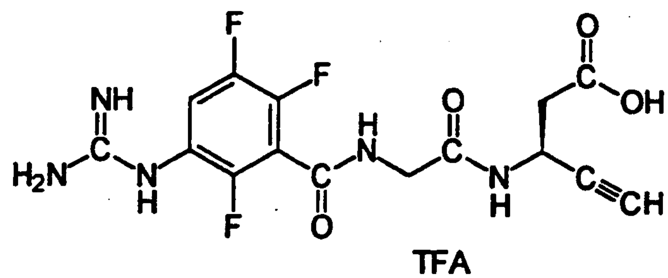
Preparation of βS-[[2-[[[3-[[imino(1-pyrrolidinyl)-methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to methodology of Example 24, substituting an equivalent amount of pyrrolidine for benzylamine in Example 23, Step B and an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and further used in Example 1, Step D as described in Example 23, Step C.

Example 35

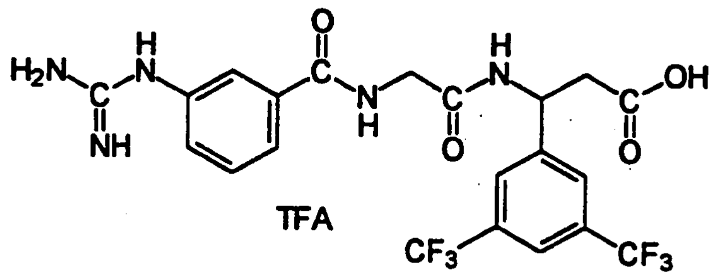
Preparation of βS-[[2-[[[3-[(aminoimin methyl)amino]-2,5,6-trifluorophenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 2, substituting an equivalent amount of ethyl 3-S-amino-4-pentynoate hydrochloride for ethyl DL-3-amino-3-(3-pyridyl)propionate dihydrochloride in Example 1, Step C and substituting an equivalent amount of 3-amino-2,5,6-trifluorobenzoic acid for 3-aminobenzoic acid in Example 1, Step E.

Example 36

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt



TFA

Step A

Preparation of ethyl (±) β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-bis(trifluoromethyl)benzenepropanoate.

The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of 3,5-bis-trifluoromethylbenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Step A.

NMR and mass spectrometry were consistent with the desired structure.

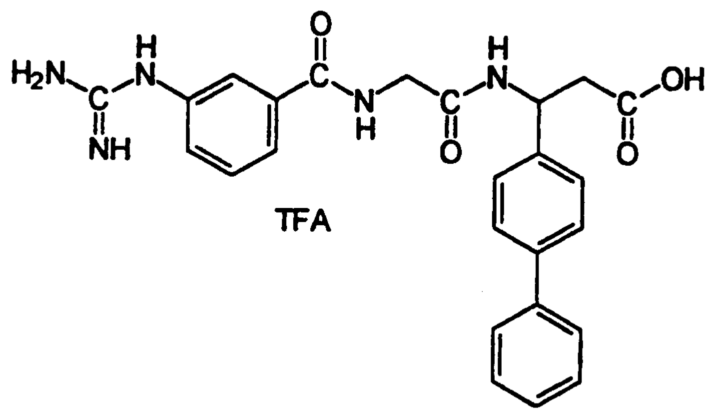
Step B

To 260 mg (0.00039 mole) of the product of Step A above in H_2O (25 ml) and CH_3CN (10 ml) was added LiOH (41 mg, 0.00098 mole). The reaction was stirred at room temperature for 1 hour. The pH was lowered to 3 with TFA and the product was isolated by reverse phase prep HPLC to yield (after lyophilization) 210 mg of the title compound as a white solid.

NMR and mass spectrometry were consistent with the desired structure.

Example 37

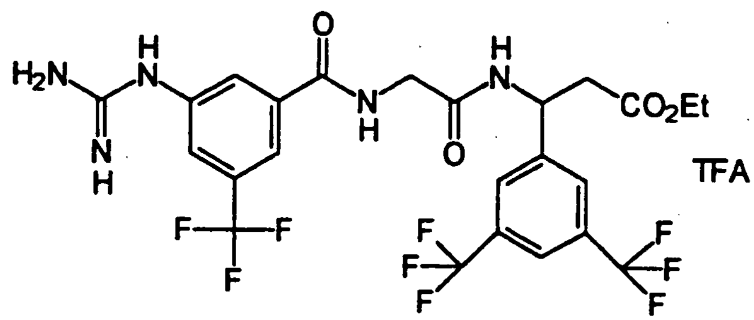
Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino][1,1'-biphenyl]-4-propanoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 2, substituting an equivalent amount of 4-biphenylcarboxaldehyde for 3-pyridinecarboxaldehyde in Example 1, Step A.

Example 38

Preparation f (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)amino]-5-(trifluoromethyl)-phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoate, trifluoroacetate salt

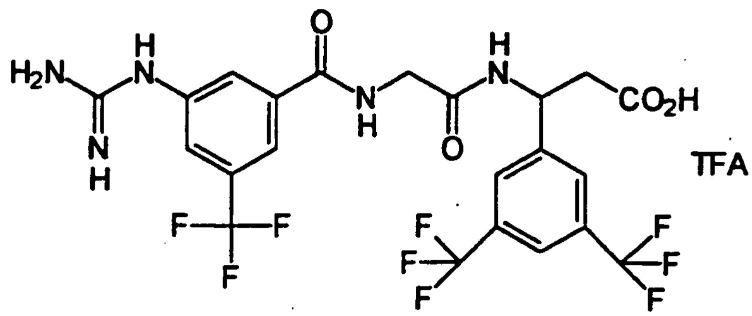


The above compound was prepared according to the methodology of Example 1, substituting the equivalent amount of 3,5-bis-trifluoromethylbenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Step A and substituting the equivalent amount of 3-amino-5-trifluoromethylbenzoic acid [which was synthesized by reduction of 3-nitro-5-trifluoromethylbenzoic acid (Lancaster) in ethanol with 10% Pd/C under 50 psi H_2 for 4 hours] for 3-aminobenzoic acid in Step E and stirring the resulting reaction mixture from Step E at reflux overnight instead of 2.5 hours.

NMR and mass spectrometry were consistent with the desired structure.

Example 39

Preparation of (±) β-[[2-[[[3-[(aminoiminom thyl)-amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]-acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt

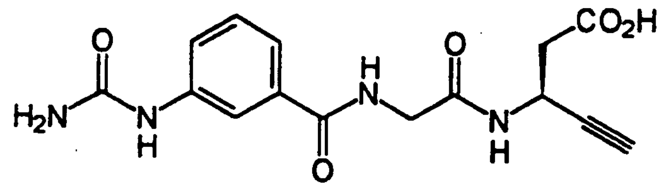


To 600 mg (0.00082 mole) of the product of Example 38 in 12 ml of H_2O and 12 ml of CH_3CN was added 140 mg (0.0033 mole) of LiOH. The reaction was stirred at room temperature for 1.5 hours. The pH was lowered to 2.5 with TFA and the product isolated by reverse phase prep HPLC to yield (after lyophilization) 520 mg of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt as a white solid.

NMR and mass spectrometry were consistent with the desired structure.

Example 40

Preparati n of 3S-[[2-[[[3-(aminocarb nylamino)-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid



Step A

Ethyl 3S-amino-4-pentynoate hydrochloride was prepared using the method in J. Med. Chem. 1995, 38, 3378-94.

Step B

2 g m-aminohippuric acid in 5% aqueous HCl (25 ml) was treated with urea (2 g) and the solution was refluxed for 4 hours. m-N-carbamoylaminohippuric acid was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized to give 1.2 g of white solid. The MS was consistent with the desired product.

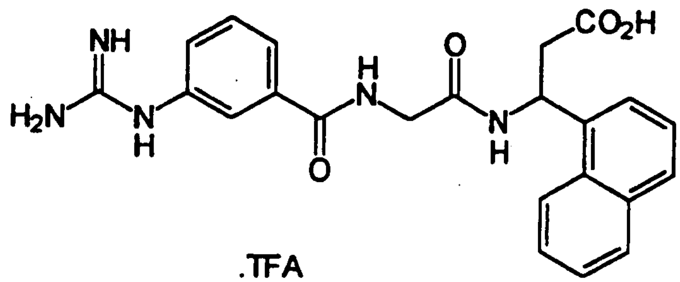
Step C

A suspension of m-ureahippuric acid (1.2 g) in DMF (5 ml) and pyridine (5 ml) was treated with DSC (1.5 g). A catalytic amount of DMAP was added and the reaction mixture was stirred for 3 hours. A solution of 3S-aminopentynoic acid, hydrochloride (0.8 g) and K_2CO_3 (0.7 g) in saturated aqueous $NaHCO_3$ (5 ml) was added to the reaction mixture. The resulting mixture was stirred overnight at room temperature. The reaction was diluted to 45 ml with 1:1 $CH_3CN:H_2O$ and acidified with of trifluoracetic acid (5 ml). The ester was purified by HPLC (RP-CH_3CN/H_2O) and a white solid (125 mg) was recovered after lyophilization. This material was then treated with 1:1 $CH_3CN:H_2O$ (20

ml) and made basic (pH>12) with LiOH. After complet reacti n, the product was purified by HPLC (RP-CH_3CN/H_2O) and th desired product (60 mg) was obtained. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 41

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]naphthalene-1-propanoic acid, trifluoroacetate salt



Step A

A mixture of freshly distilled 1-napthalenecarboxaldehyde (8.6 g), ammonium acetate (10.6 g) and malonic acid (5.7 g) in isopropyl alcohol (50 ml) was refluxed for 4 hours. The reaction was filtered while hot and washed with hot isopropyl alcohol (2 x 50 ml), washed with H_2O (125 ml) and isopropanol (100 ml) and dried *in vacuo* at 40°C. 4.6 g of βS-aminonaphthalene-1-propanoic acid as a white solid was isolated. MS and ^1H-NMR were consistent with the desired product.

Step B

A suspension of the product of Step A (4.6 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight and the excess solvent was removed under reduced pressure. The oil was dissolved into 1:1 $CH_3CN:H_2O$ and purified by HPLC (RP-CH_3CN/H_2O). Methyl βS-aminonaphthalene-1-propanoate (4.6 g) as a white solid was obtained. MS and ^1H-NMR were consistent with the desired product.

Step C

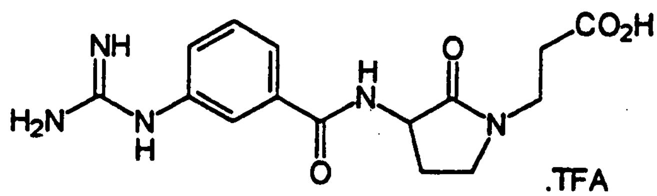
A suspension of m-guanidinohippuric acid HCl (1.4 g) in DMF (5 ml) and pyridine (5 ml) was treat d with DSC (3 g) and a catalytic amount of DMAP. The reaction was stirred overnight at room temperature. The resulting solution was treated with a solution of the product of Step B (1.7 g) and NMM (0.6 ml) in DMF (2.5 ml) and pyridine (2.5 ml). The mixture was stirred overnight at room temperature. The reaction was then treated with TFA and diluted to 50 ml with 1:1 $CH_3CN:H_2O$. The solution was purified by HPLC (RP-CH_3CN/H_2O) and (±) methyl βS-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]naphthalene-1-propanoate (1.3 g) as a white solid was obtained after lyophilization. MS and ^{1}H-NMR were consistent with the desired product.

Step D

A solution of the product of Step C (0.5 g) in 1:1 $CH_3CN:H_2O$ (15 ml) was treated with LiOH until pH > 12. The reaction was monitored by HPLC (RP-CH_3CN/H_2O) and when hydrolysis was complete, the desired material was purified by HPLC (RP-CH_3CN/H_2O). A white solid (0.3 g) was recovered after lyophilization. MS, ^{1}H-NMR and CHN were consistent with the desired product.

Example 42

Preparation of (±) 3-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]-2-oxopyrrolidine-1-propanoic acid, trifluoroacetate salt

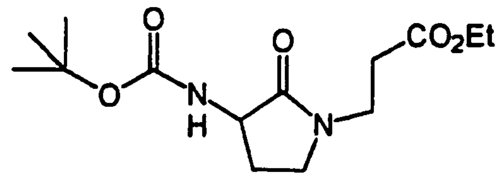


Step A

A solution of N-(tert-butoxycarbonyl)-L-methionine (6.2 g) in DMF (25 ml) and pyridine (25 ml) was treated with DSC (9.6 g) and a catalytic amount of DMAP. After 4 hours, a solution of β-alanine ethyl ester HCl (3.8 g) and K_2CO_3 (3.5 g) in saturated aqueous $NaHCO_3$ (25 ml) was added. The reaction mixture was stirred overnight at room temperature. The excess solvent was removed under reduced pressure and purified by HPLC (RP-CH_3CN/H_2O). N-[2-[[(1,1-dimethylethoxy)carbonyl]-amino]-4-(methylthio)-1-oxobutyl]-β-alanine, ethyl ester (7.0 g) as a colorless oil was obtained. The oil was confirmed as the desired product by MS and used without further purification.

Step B

6.5 g of the oil from Step A was dissolved in DMF (25 ml) and treated with CH_3I (5.0 ml). After approximately 1 hour, NaH (0.50 g) was added, followed by further addition of NaH (0.50 g). The reaction was treated with H_2O (25 ml) and EtOAc (200 ml). The organic layer was washed with additional H_2O (3 x 25 ml), saturated aqueous NaCl (1 x 25 ml) and dried over $NaSO_4$. The excess solvent was r moved under reduced pressure to give 4 g of



as a tan semi-solid. MS was consistent with the structure and the product was used without further purification.

Step C

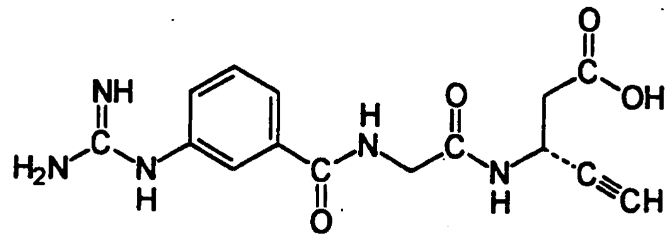
A solution of the product of Step B (4 g) in ethanol (50 ml) was treated with 4N HCl/dioxane (20 ml). The excess solvent was removed under reduced pressure. The crude solid was purified by HPLC (RP-CH_2CN/H_2O). 20% aqueous HCl (10 ml) was added and 1 g of ethyl 3-amino-2-oxopyrrolidine-1-propanoate was obtained as a white solid after lyophilization. MS was consistent with the desired product.

Step D

A solution of m-guanidinobenzoic acid HCl (0.7 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (0.8 g) and a catalytic amount of DMAP. After 3 hours a solution of the product of Step C (0.7 g) in H_2O (3 ml) with an equal molar amount of K_2CO_3 was added. The reaction was stirred overnight at room temperature. The desired ester was isolated by HPLC (RP-CH_3CN/H_2O). The white solid (100 mg) was treated with H_2O (10 ml) and made basic with LiOH (pH>12). After 2 hours, the desired product was isolated by HPLC (RP-CH_3CN/H_2O) and lyophilized. 75 mg of (±) 3-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]-2-oxopyrrolidine-1-propanoic acid, trifluoroacetate salt as a white solid was obtained. MS, ^{1}H-NMR and CHN analysis were consistent with th d sired product.

Example 43

Preparation of 3R-[[2-[[[3-[(amin iminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, hydrochloride salt



Step A

Ethyl 3-(N-(tert-butoxycarbonyl)amino)pent-4-ynoic ester (3 g) [J. Med. Chem., 1995, 38, 3378-94] in CH_2Cl_2 (60 ml) at 0°C was treated with TFA (30 ml). The reaction was stirred for 3 hours. The excess solvent was removed under reduced pressure and a yellow oil (3.3 g) was obtained. The oil was confirmed as the desired product by MS.

Step B

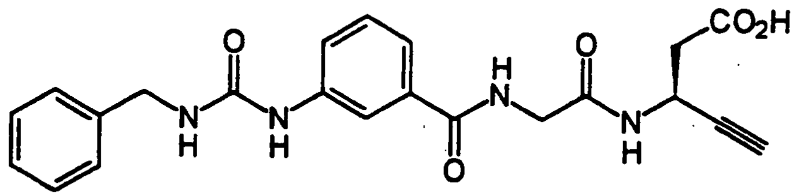
A solution of m-guanidinohippuric acid HCl (3.3 g) in DMF (12 ml) and pyridine (12 ml) was treated with DSC (6.1 g) and a catalytic amount of DMAP. After 3 hours, a solution of crude product (3.3 g) from Step A in saturated aqueous $NaHCO_3$ (12 ml) was added. The reaction was stirred overnight at room temperature. The excess solvent was removed under reduced pressure. The resulting solid was treated with TFA and 1:1 CH_3CN:H_2O. The product was isolated by HPLC (RP-CH_3CN/H_2O) to yield ethyl 3R-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]propynoate trifluoroacetate salt (3 g) as a white s lid. MS and ^1H-NMR were consistent with the desired product.

Step C

The product of Step B (3 g) was dissolved in 1:1 $CH_3CN:H_2O$ (50 ml) and treated with LiOH (pH>12). Aft r 4 hours the reaction was acidified with TFA and the TFA salt of the desired product was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.5 g) was slurried with 1:3 $CH_3CN:H_2O$ (100 ml) and ion exchange resin, AG 2-X8 chloride form (BioRad)(50 g). The mixture was filtered and treated with 20% HCl (5 ml). The clear solution was lyophilized and the resin exchange process was repeated. The desired product (2.2 g) was obtained. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 44

Pr paration of 3S-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid



Step A

m-Aminohippuric acid HCl (20 g) in CH_3CN (100 ml) was treated with benzyl isocyanate (16 ml). The reaction was treated with 5% aqueous HCl (400 ml), filtered and washed with H_2O (50 ml) to give 21 g of m-(benzylurea)hippuric acid. The MS and ^1H-NMR were consistent with the desired product. No further purification was done.

Step B

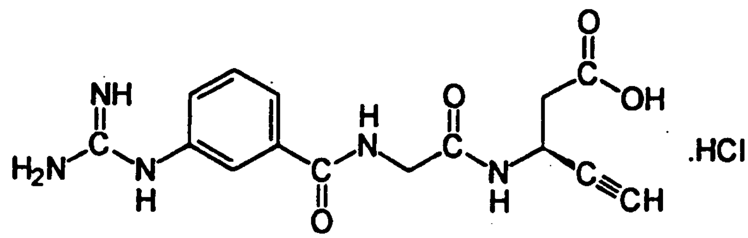
Ethyl 3S-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoate was prepared using the method in Example 40 substituting an equal molar amount of m-(benzylurea)hippuric acid for m-ureahippuric acid. The desired ester was purified by HPLC (RP - CH_3CN/H_2O) to give 1.2 g as a white solid. The MS and ^1H-NMR were consistent with the desired ester.

Step C

A solution of ethyl 3S-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-4-pentynoate (1.0 g) in 1:1 $CH_3CN:H_2O$ (20 ml) was treated with KOH (pH>12). After 4 hours the reaction was acidifi d with TFA and purifi d twice by HPLC (RP-CH_3CN/H_2O). A white solid (300 mg) was btained. MS, ^1H-NMR and CHN were consistent with the desired product.

Example 45

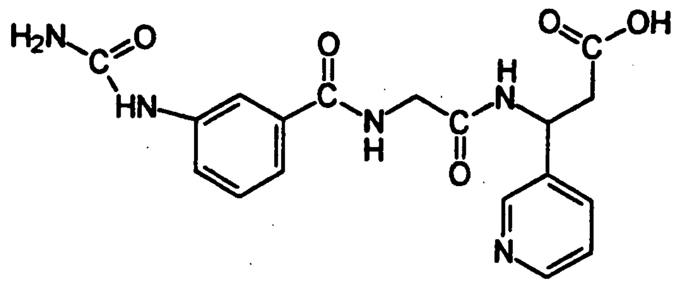
Preparation of 3S-[[2-[[[3-[(amin iminom thyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, hydrochloride salt



The product of Example 58 (6 g) was dissolved in 1:1 $CH_3CN:H_2O$ (75 ml) and treated with KOH. The pH was maintained greater than 12 by addition of KOH. After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The TFA salt (4.2 g) was obtained after the appropriate fractions were lyophilized. The solid was slurried in 1:1 $CH_3CN:H_2O$ (100 ml) and treated with ion exchange resin AG 2-X8 chloride form (BioRad) (50 g). The mixture was filtered and treated with 20% HCl (5 ml). After lyophilization the resin exchange was repeated. The desired product as the HCl salt (3.5 g) was obtained. MS, ^1H-NMR and CHNCl were consistent with the desired product.

Example 46

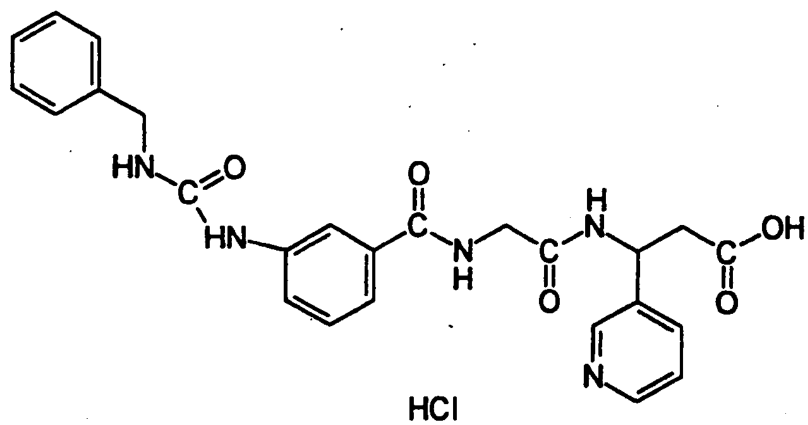
Preparation of β-[[2-[[[3-(aminocarbonylamino)phenyl]-carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, hydrochloride salt



Urea (4 g) and ethyl β-[[2-[[(3-aminophenyl)-carbonyl]amino]acetyl]amino]pyridine-3-propanoate trifluoroacetate salt (4 g) were dissolved in 20% aqueous HCl (50 ml) and refluxed for 6 hours. The reaction was made basic with KOH (pH>12). After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The white solid was dissolved in 1:1 $CH_3CN:H_2O$ (100 ml) and subjected to the resin exchange described in Example 43, Step C. Lyophilization gave the desired product (3.2 g). MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 47

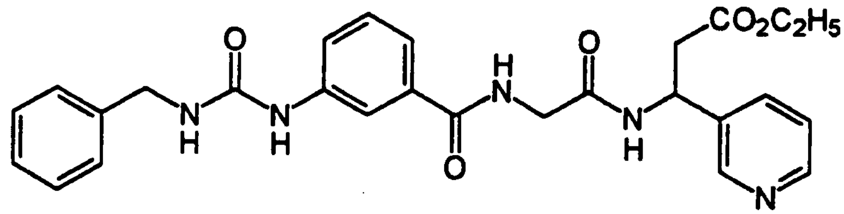
Preparation of (±) β-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, hydrochloride salt



The product of Example 48 (5 g) was dissolved in 1:1 CH_3CN:H_2O (75 ml) and treated with KOH. The pH was maintained greater than 12 by addition of KOH. After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The TFA salt (4.5 g) was obtained after lyophilization. The solid was slurried in 1:1 CH_3CN:H_2O (100 ml) and ion exchange resin, AG 2-X8 chloride form (BioRad)(50 g). The mixture was filtered and treated with 20% HCl (5 ml). After lyophilization the resin exchange process was repeated. The desired product (4.1 g) was obtained as a white solid. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 48

Preparation of (±) ethyl β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoate, hydrochloride salt



Step A

A solution of m-nitrohippuric acid (5.6 g) in DMF (25 ml) was treated with DSC (9.6 g) and a catalytic amount of DMAP. After 5 hours, a solution of ethyl 3-amino-3-(3-pyridyl)propanoate 2HCl (8 g) and K_2CO_3 (2 g) in saturated aqueous $NaHCO_3$ (25 ml) was added. The reaction mixture was stirred overnight at room temperature. H_2O (25 ml) was added and the mixture was filtered. The resulting solid was washed with H_2O (25 ml), slurried with CH_3CN (25 ml) and filtered. Ethyl β-[[2-[[(3-nitrophenyl)carbonyl]amino]acetyl]amino]pyridine-3-propanoate (6.5 g) was obtained as a white solid. MS was consistent with the desired product.

Step B

A suspension of the product of Step A (6.5 g) and 5% Pd/C (0.6 g) in H_2O (50 ml) and ethanol (50 ml) was subjected to 50 psi H_2 for 3 hours. The mixture was filtered through a celite pad and the excess solvent was removed under reduced pressure. The resulting oil was treated with CH_2Cl_2 and the solvent was again removed under reduced pressure. Ethyl β-[[2-[[(3-aminophenyl)carbonyl]amino]acetyl]amino]pyridine-3-

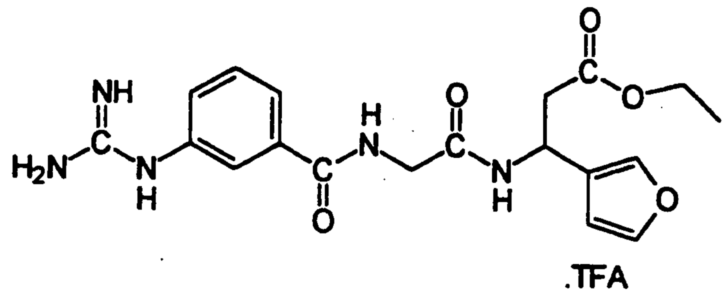
propanoate (5.8 g) was recovered as a tan foam. MS and ^{1}H-NMR were consistent with th desir d product.

Step C

A solution of the product of Step B (1.9 g) in CH_3CN (5 ml) was treated with benzyl isocyanate (0.8 ml). After 1 hour benzyl isocyanate (0.1 ml) was added to complete the reaction. After 0.25 hour the reaction was treated with H_2O (50 ml). The resulting viscous oil was dissolved in CH_3CN and was acidified with TFA. The solution was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized. The white solid was repurified by HPLC (RP-CH_3CN/H_2O) and treated with 20% HCl (5 ml). The desired product (1.3 g) was obtained as a white solid. MS, ^{1}H-NMR and CHNCl were consistent with the desired product.

Example 51

Preparation of (±)ethyl β-[[2-[[[3-[(aminoimin m thyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-3-propanoate, trifluoroacetate salt



Step A

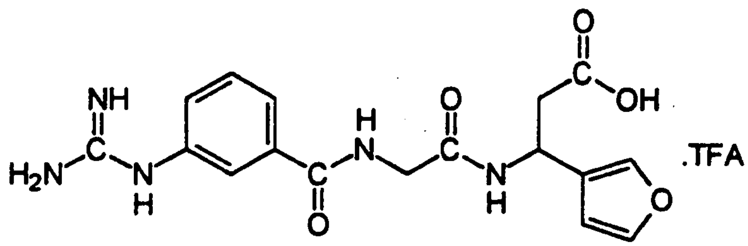
A suspension of 3-furancarboxaldehyde (8.6 ml), malonic acid monoethyl ester (15.8 g) and ammonium acetate (9.6 g) in isopropyl alcohol (200 ml) was heated to reflux under nitrogen. After 5 hours, the excess solvent was removed under reduced pressure and the semi-solid was treated with H_2O (250 ml) and acidified to pH 2 using 12N HCl. The aqueous layer was washed with CH_2Cl_2 (2 x 100 ml). The aqueous layer was neutralized to pH >9 with K_2CO_3. The product was extracted with CH_2Cl_2 (2 x 100 ml). The organic layer was dried over Na_2SO_4 and the excess solvent was removed under reduced pressure to give ethyl β-aminofuran-3-propanoate (5 g) as a golden oil. The MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (1.4 g) in DMF (5 ml) and pyridine (5 ml) was treated with DSC (1.9 g) and a catalytic amount of DMAP. After 5 hours, to a solution of the product of Step A (1.2 g) in CH_3CN (1 ml) was added saturated aqueous $NaHCO_3$ (1 ml). The mixture was stirred overnight at room temperature and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (1.2 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 52

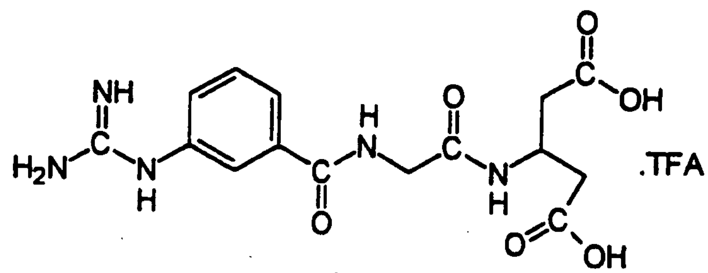
Preparation of (±) β-[[2-[[[3-[(amin iminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-3-propanoic acid, trifluoroacetate salt



The product of Example 51 (0.6 g) was dissolved in 1:1 $CH_3CN:H_2O$ (15 ml) and was treated with NaOH (pH>12). After 4 hours the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (0.3 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 53

Preparation of 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pentanedioic acid, trifluoroacetate salt



Step A

Dimethyl 3-ketoglutarate (13 g) in methanol (50 ml) was treated with ammonium formate (5 g) and $NaCNBH_3$ (2 g). 10 ml of H_2O was added and the excess solvent removed under reduced pressure. The semi-solid was dissolved in 5% aqueous HCl (250 ml), and washed with CH_2Cl_2 (2 x 50 ml). The aqueous layer was made basic (pH>9) with K_2CO_3 and the product was extracted using CH_2Cl_2 (2 x 75 ml). The organic layers were combined and dried with Na_2SO_4. The excess solvent was removed to give 2.5 g of the dimethyl (±)3-aminoglutarate. This was dissolved in methanol (50 ml) and treated with 4N HCl/Dioxane (10 ml). The excess solvent was removed under reduced pressure to give a 2.7 g of dimethyl (±)3-aminoglutarate hydrochloride. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (1.5 g) in DMF (4.5 ml) and pyridine (4.5 ml) was treated with DSC (1.8 g) and a catalytic amount of DMAP. After 2 hours, a solution of dimethyl 3-aminoglutarate HCl (1.1 g) and NMM (350 µl) in H_2O (3 ml) was added to the reaction. The reaction was stirred overnight at room temperature and the product was isolated by HPLC. 1.5 g of 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-

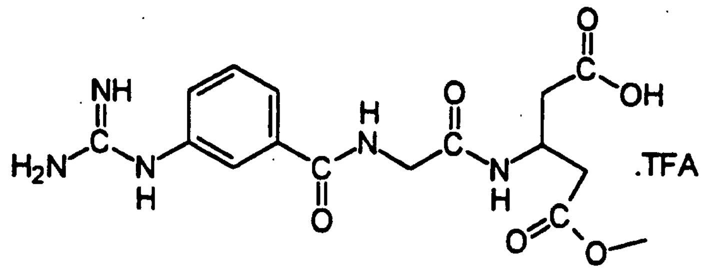
carbonyl]amino]acetyl]amino]pentan dioic acid, bismethyl ester was obtained as a whit solid. MS and ^{1}H-NMR were consistent with the desired product.

Step C

The product of Step B (750 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (40 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (400 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 54

Preparation of (±) hydrogen methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]pentanedioate, trifluoroacetate salt



Step A

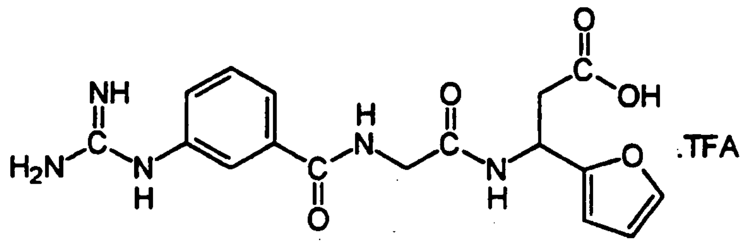
A solution of m-guanidinohippuric acid HCl (1.5 g) in DMF (4.5 ml) and pyridine (4.5 ml) was treated with DSC (1.8 g) and a catalytic amount of DMAP. After 2 hours, a solution of dimethyl 3-aminoglutarate HCl (1.1 g) and NMM (350 μl) in H_2O (3 ml) was added to the reaction. The reaction was stirred overnight at room temperature and the product was isolated by HPLC. 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]pentanedioic acid, bis methyl ester (1.5 g) as a white solid was obtained. MS and ^{1}H-NMR were consistent with the desired product.

Step B

750 mg of the product of Step A was dissolved in Na_2PO_4 buffer (50 ml, 50 mM, pH 8.5) and treated with porcine esterase (200 μl). The pH was adjusted using LiOH. After 48 hours, the solution was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^{1}H-NMR and CHN analysis consistent with the desired product.

Example 55

Preparati n f (±) β-[[2-[[[3-[(amin imin methyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-2-propanoic acid, trifluoroacetate salt



Step A

A suspension of 2-furancarboxaldehyde (4.8 g), ammonium acetate (9.6 g) and malonic acid monoethyl ester (6.6 g) in isopropanol (50 ml) was refluxed for 6 hours. The excess solvent was removed under reduced pressure and the resulting oil was treated with ethyl acetate (100 ml) and 5% aqueous HCl (400 ml). The aqueous layer was then washed with ethyl acetate (100 ml). The aqueous layer was made basic with K_2CO_3 (pH 9). The product was extracted with CH_2Cl_2 (2 x 100 ml). The organic layers were combined and dried with Na_2SO_4 and the excess solvent was removed. Ethyl β-aminofuran-2-propanoate (2.5 g) as a dark oil was recovered. MS and ^{1}H-NMR were consistent with the desired product. The dark oil was treated as described in Example 53, Step A to give 2.7 g of ethyl β-aminofuran-2-propanoate hydrochloride.

Step B

A solution of m-guanidinohippuric acid HCl (272 mg) in DMF (1 ml) and pyridine (1 ml) was treated with DSC (450 mg) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step A (221 mg), NMM (111 μl) in H_2O (1 ml) and CH_3CN (1 ml) was added. Th reaction was stirred overnight at room temp ratur .

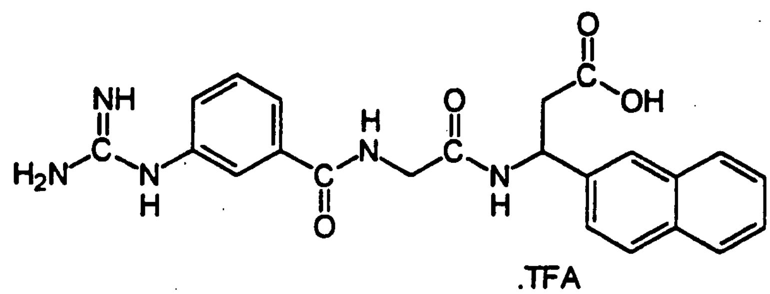
(±) Ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]furan-2-propanoate was purified by HPLC (RP-CH_3CN/H_2O) and lyophilized to give a white solid (200 mg). MS was consistent with the desired product.

Step C

The product of Step B (200 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with LiOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 56

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]naphthalene-2-propanoic acid, trifluoroacetate salt



Step A

A suspension of 2-naphthaldehyde (7.8 g) and ammonium acetate (9.6 g) in isopropyl alcohol (50 ml) was heated for 1 hour at reflux. Malonic acid (5.2 g) was added and reflux was continued for 3 hours. The reaction was filtered while hot and the solid washed with hot isopropyl alcohol (50 ml) followed by CH_3CN (100 ml). The white solid was dried overnight *in vacuo* and β-aminonaphthalene-2-propanoic acid (9 g) was recovered. MS and ^{1}H-NMR were consistent with the structure.

Step B

A suspension of the product of Step A (2.5 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The resulting solution was stirred overnight. The excess solvent was removed under reduced pressure and the semi solid was purified by HPLC (RP-CH_3CN/H_2O). The solid was dissolved in CH_3CN/H_2O, treated with 20% aqueous HCl (5 ml) and lyophilized to give methyl β-aminonaphthalene-2-propanoate hydrochloride (1.1 g). MS and ^{1}H-NMR wer consistent with the structure.

Step C

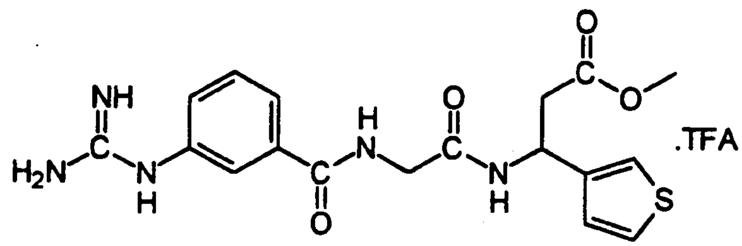
A solution of m-guanidinohippuric acid (0.7 g) in DMF (4 ml) and pyridine (4 ml) was tr at d with DSC (1.1 g) and a catalytic amount of DMAP. After 4 hours, a solution of the product of Step B (0.9 g), NMM (0.4 ml) in DMF (2 ml), pyridine (2 ml) and H_2O (1 ml) were added. The reaction was stirred overnight at room temperature and acidified with TFA. The desired product was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (0.7 g) had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Step D

The product of Step C (200 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (175 mg) had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Example 57

Preparation of (±) methyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]thiophene-3-propanoate, trifluoroacetate salt



Step A

A solution of 3-thiophenecarboxaldehyde (11.2 g) in isopropanol (100 ml) was treated with ammonium acetate (20 g). The resulting mixture was heated and malonic acid (10.4 g) was added. The reaction was refluxed for 4 hours and filtered while hot. The solid was washed with hot isopropanol (2 x 50 ml) and dried *in vacuo* overnight at 40°C. 8 g of β-aminothiophene-3-propanoic acid was recovered. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A suspension of the product of Step A (5 g) in methanol (100 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight. The excess solvent was removed under reduced pressure. Methyl β-aminothiophene-3-propanoate hydrochloride (7.8 g) was isolated as a yellow foam. MS and ^{1}H-NMR were consistent with the desired product.

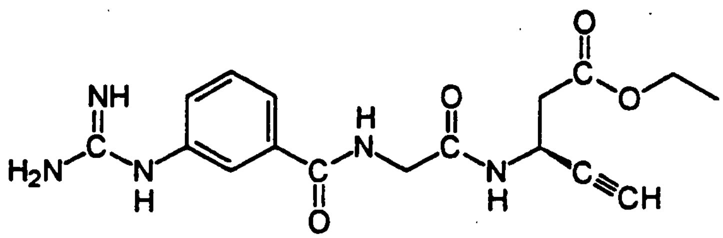
Step C

A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) and pyridine (10 ml) was treated with DSC (4.5 g) and a catalytic amount of DMAP. After 4 hours, a solution of the product of St p B (2.2 g) and

NMM (1.3 ml) in DMF (5 ml) was added and the reaction was stirred overnight at room temperature. The reaction mixture was treated with 1:1 $CH_3CN:H_2O$ (50 ml) and acidified with TFA. The desired compound was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.2 g) had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Example 58

Preparation of ethyl 3S-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoate, trifluoroacetate salt

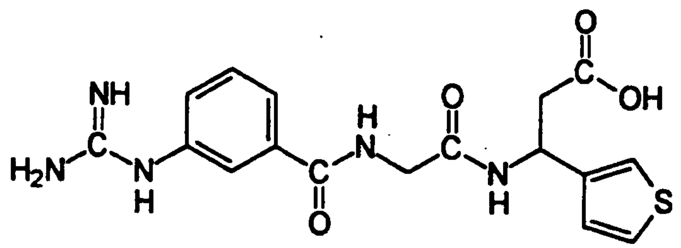


.TFA

A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) and pyridine (10 ml) was treated with DSC (4.5 g) and a catalytic amount of DMAP. After 4 hours, a solution of ethyl 3S-amino-4-pentynoic acid, hydrochloride (1.8 g) and NMM (1.1 ml) in DMF (5 ml) was added and the reaction was stirred overnight at room temperature. The reaction mixture was treated with 1:1 CH_3CN:H_2O (50 ml) and acidified with TFA. The desired compound was isolated by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (2.6 g) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 59

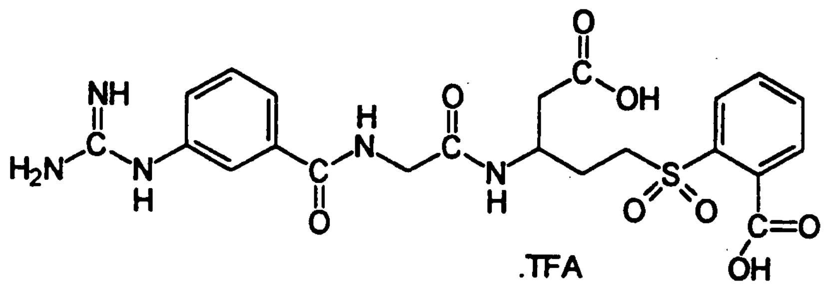
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]thiophene-3-propanoic acid, trifluoroacetate salt



The product of Example 57 (750 mg) was dissolved in 1:1 $CH_3CN:H_2O$ (20 ml) and treated with KOH (pH>12). After 4 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (500 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 60

Preparation of (±) 2-[3-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-carboxybutyl]sulfonyl]benzoic acid, trifluoroacetate salt



Step A

A solution of 2-[(3-amino-4-carboxybutyl)thio]-benzoic acid (1 g) (prepared according to U.S. 5,409,939) in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml) overnight. The excess solvent was removed under reduced pressure to give the desired product (0.9 g). MS of the white solid, methyl 2-[(3-amino-4-(methoxycarbonyl)butyl]thio]benzoate was consistent with the proposed structure.

Step B

A solution of m-guanidinohippuric acid HCl (0.8 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (1.2 g) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step A (1 g), NMM (0.3 ml) in DMF (3 ml) was added. The reaction was stirred overnight at room temperature. KOH was added until pH greater than 12. After 4 hours, the reaction was acidified and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid, (±) 2-[3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-carboxybutyl]thio]benzoic acid,

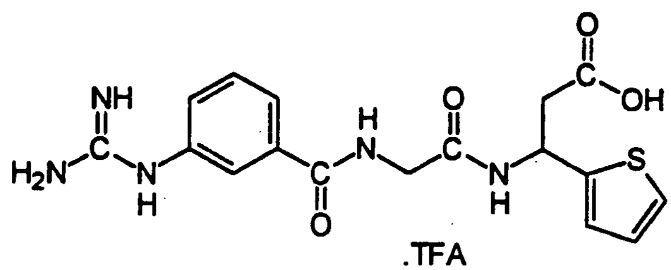
trifluoroacetate salt (750 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Step C

A solution of the product of Step B (320 mg) in 1:1 $CH_3CN:H_2O$ (50 ml) was treated with m-chloroperoxybenzoic acid (340 mg). The reaction was stirred overnight at room temperature and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid (300 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 61

Preparation f (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]thiophene-2-propanoic acid, trifluoroacetate salt



Step A

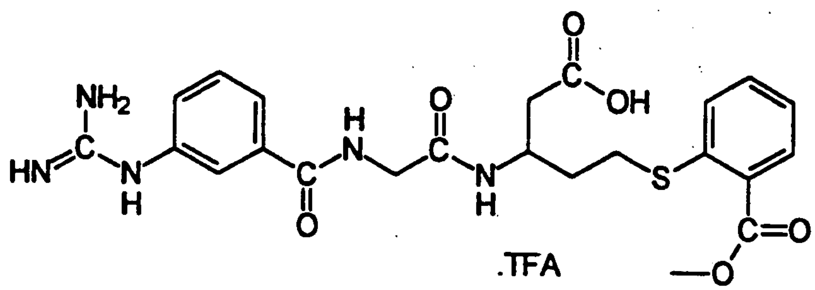
A solution of 3-amino-3-(2-thienyl)propanoic acid (0.5 g) [prepared substituting a molar equivalent amount of 2-thiophene-carboxaldehyde in Example 57, Step A] in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml). After 6 hours the excess solvent was removed under reduced pressure to give a waxy solid. Treatment with Et_2O/CH_3CN produced methyl β-aminothiophene-2-propanoate (370 mg) as a white powder. MS and ^1H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (0.4 g) in DMF (1.5 ml) and pyridine (1.5 ml) was treated with DSC (0.6 g) and a catalytic amount of DMAP. After 3 hours, a solution of the product of Step A (0.3 g) and NMM (220 μl) in DMF (1.5 ml) was added. The reaction was stirred overnight at room temperature. The ester was isolated by HPLC (RP-CH_3CN/H_2O) and lyophilized. The resulting white solid was treated with KOH (pH>12) in 1:4 $CH_3CN:H_2O$. After 4 hours, the reaction was acidified by TFA and purified by HPLC (RP-CH_3CN/H_2O). Th lyophilized solid (300 mg) had MS, ^1H-NMR and CHN analysis that were consistent with the desired product.

Example 62

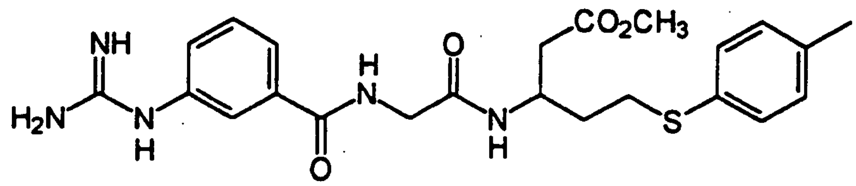
Preparation of (±) methyl 2-[[3-[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-carboxybutyl]thio]benzoate, trifluoroacetate salt



A solution of m-guanidinohippuric acid HCl (0.8 g) in DMF (3 ml) and pyridine (3 ml) was treated with DSC (1.2 g) and a catalytic amount of DMAP. After 2 hours, a solution of methyl 2-[[3-amino-4-(methoxycarbonyl)-butyl]thio]benzoate (1 g) [prepared according to U.S. 5,409,939], NMM (0.3 ml) in DMF (3 ml) was added. The reaction was stirred overnight at room temperature. KOH was added until the pH was greater than 12. After 2 hours, the reaction was acidified and purified by HPLC (RP-CH_3CN/H_2O). The lyophilized solid, (250 mg) had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 63

Preparation of (±) methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-5-[(4-methylphenyl)thio]pentanoate, trifluoroacetate salt



Step A

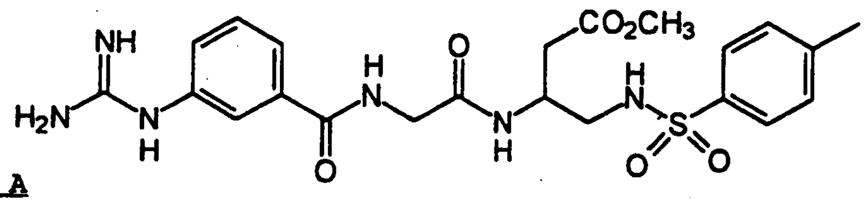
A solution of 3-amino-5-[(4-methylphenyl)-thio]pentanoic acid (1.0 g) [prepared according to U.S. 5,409,939] in methanol (50 ml) was treated with 4N HCl/dioxane (10 ml). The reaction was stirred overnight at room temperature. The excess solvent was removed under reduced pressure. Methyl 3-amino-5-[(4-methylphenyl)thio]pentanoate (1.1 g) as a white solid was obtained. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (0.6 g) in DMF (2 ml) and pyridine (2 ml) was treated with DSC (0.7 g) and a catalytic amount of DMAP. After 1 hour, a solution of the product of Step A (0.6 g) in saturated aqueous $NaHCO_3$ (1.5 ml) and acetonitrile (1.5 ml) was added. The reaction was stirred for 2 hours at room temperature. The reaction was acidified with TFA and the title compound (0.6 g) was isolated by HPLC as a white solid. MS and ^{1}H-NMR were consistent with the desir d product.

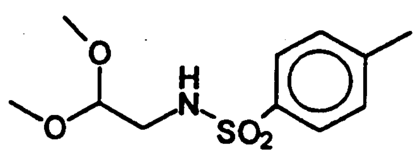
Example 64

Preparation f (±) methyl 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-4-[[(4-methylphenyl)sulfonyl]amino]butanoate, trifluoroacetate salt



Step A

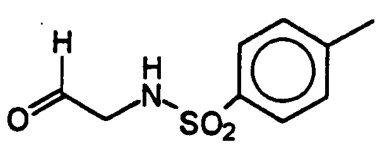
A mixture of aminoacetaldehyde dimethyl acetal (15.8 g), p-toluenesulfonylchloride (19.1 g) and Et_3N (10.1 g) in CH_2Cl_2 (200 ml) was stirred for 2 hours. The reaction was treated with 5% aqueous HCl (50 ml) and Et_2O (200 ml). The layers were separated and the organic layer was washed with 5% aqueous HCl (50 ml), H_2O (50 ml) and dried over Na_2SO_4. The excess solvent was removed under reduced pressure to give 30 g of the desired acetal;



confirmed by MS and ^1H-NMR.

Step B

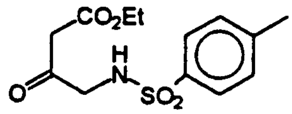
A mixture of the acetal from Step A (10 g), CH_3CN (70 ml) and aqueous HCl (15 ml) was heated to 50°C for 10 minutes. Diethylether was added and the desired aldehyde was extracted. The aldehyde was then used without further purification. The desired aldehyde



was verified by MS.

Step C

A mixture f ethyldiazoacetat (2.3 g), $SnCl_2$ (2.5 g) in CH_2Cl_2 (75 ml) was treated with the aldehyde from Step B (5 g). After 2 hours, aqueous HCl and Et_2O were added. The organic layer was separated and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield 5 g of crude β-keto ester

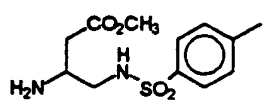


; confirmed by MS and ^{1}H-NMR and used without further purification.

Step D

The β-keto ester from Step C (12 g), methanol (100 ml), H_4N^+ HCO_2^- (30 g) and $NaCNBH_3$ (1.3 g) was stirred. After 24 hours, the excess solvent was removed under reduced pressure. The resulting semi-solid was treated with CH_2Cl_2 and the desired product was extracted using aqueous HCl. Removal of the solvent gave 6 g of crude

β-amino ester



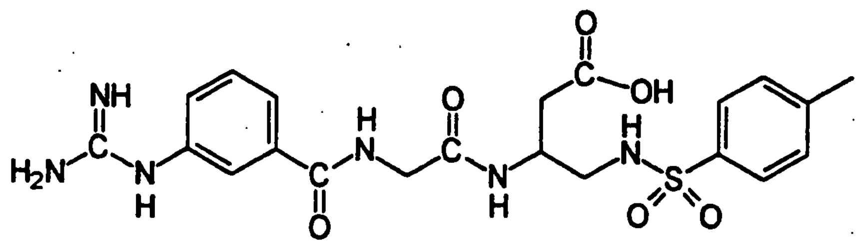
; confirmed by MS and ^{1}H-NMR.

Step E

A solution of m-guanidinohippuric acid HCl (337 mg) in DMF (1 ml) and pyridine (1 ml) was treated with DSC (0.4 g) and a catalytic amount of DMAP. After 2 hours, a solution of the product of Step D (322 mg) and NMM (220 μl) in DMF (1 ml) was added. The reaction was stirred overnight at room temperature. The reaction was acidified with TFA and the title compound (250 mg) was isolated by HPLC (RP-CH_3CN/H_2O) as a white solid. MS, CHN and ^{1}H-NMR were consistent with the desired product.

Example 65

Preparation of 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-[[(4-methylphenyl)sulfonyl]amino]butanoic acid, trifluoroacetate salt

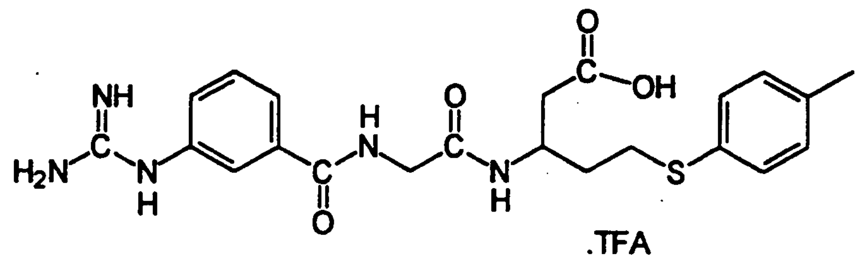


.TFA

A solution of the product of Example 64 (180 mg) in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with LiOH (100 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). The title compound (100 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 66

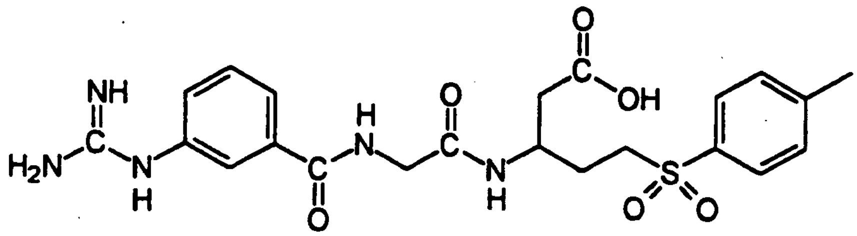
Pr paration of (±)3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)thio]pentanoic acid, trifluoroacetate salt



A solution of 180 mg of the product from Example 63 in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with LiOH (100 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-5-[(4-methylphenyl)thio]pentanoic acid, trifluoroacetate salt (100 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 67

Preparation of (±)3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)sulfonyl]pentanoic acid, trifluoroacetate salt

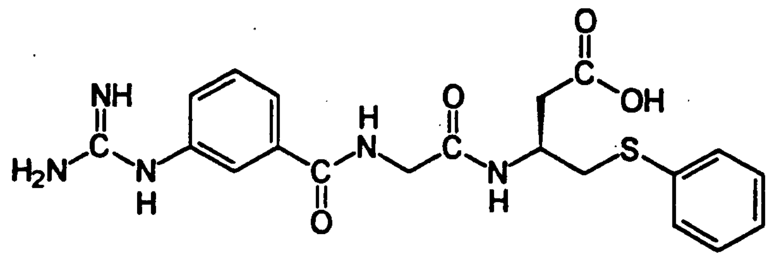


.TFA

A solution of the product from Example 63 (200 mg) in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with of m-chloroperoxybenzoic acid (460 mg). The reaction was stirred overnight at room temperature. The reaction was treated with LiOH (200 mg). After 2 hours, the reaction was acidified with TFA and purified by HPLC (RP-CH_3CN/H_2O). 3-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-[(4-methylphenyl)sulfonyl]pentanoic acid, trifluoroacetate salt (180 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHN analysis were consistent with the desired product.

Example 68

Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-(phenylthio)butanoic acid, trifluoroacetate salt



.TFA

Step A

A suspension of phenylmethyl 3S-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[(methylsulfonyl)-oxy]butanoate (3.9 g) [prepared according to U.S. 5,409,939], thiophenol (1.1 ml) and K_2CO_3 (1.4 g) in DMF (20 ml) was stirred at room temperature overnight. The reaction was treated with ethyl acetate and the organic layer was washed with H_2O (2 x 25 ml) and saturated NaCl (25 ml). The organic layer was dried with Na_2SO_4 and the excess solvent removed under reduced pressure to give a golden oil (4.5 g). The oil was dissolved in CH_2Cl_2 (100 ml) and treated with TFA (20 ml). After 4 hours the excess solvent was removed under reduced pressure and the product was purified by HPLC (RP-CH_3CN/H_2O). Phenylmethyl 3S-amino-4-(phenylthio)butanoate TFA salt (1.2 g) was isolated as a white solid. MS and ^{1}H-NMR were consistent with the desired product.

Step B

A solution of m-guanidinohippuric acid HCl (273 mg) and NMM (110 μl) in DMF (1 ml) was treated with pivaoyl chloride (120 μl). After 30 minutes, a s lution of the product from Step A (208 mg), NMM (110

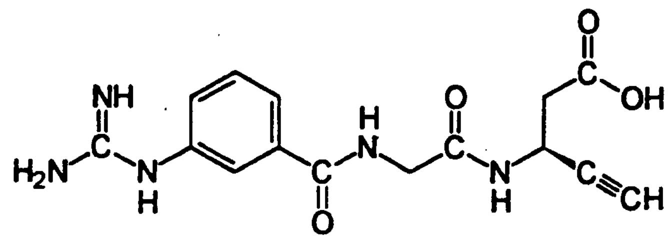
μl) and a catalytic amount of DMAP in DMF (1 ml) was added. After 4 hours, phenylm thyl 3S-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amin]ac tyl]-amino]-4-(phenylthio)butanoate (200 mg) was isolated by HPLC (RP-CH_3CN/H_2O) as a white solid. MS and ^1H-NMR were consistent with the desired product.

Step C

A solution of 200 mg of the product of Step B in 1:1 $CH_3CN:H_2O$ (4 ml) was treated with KOH (pH>12). After 2 hours, the reaction was acidified with TFA and the product was isolated by HPLC (RP-CH_3CN/H_2O). 3S-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]-4-(phenylthio)butanoic acid, trifluoroacetate salt (100 mg) was isolated as a white solid. MS, ^1H-NMR and CHN analysis were consistent with the desired product.

Example 69

Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



Step A

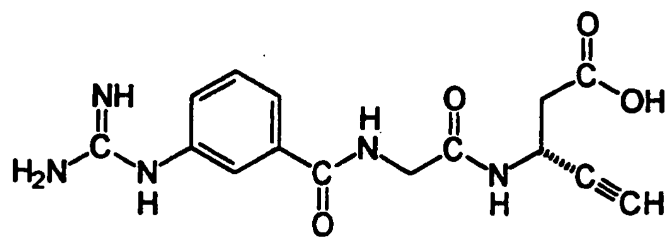
A solution of m-guanidinohippuric acid HCl (2.7 g) in DMF (10 ml) was treated with pivaoyl chloride (1.3 ml). After 30 minutes, a solution of 3S-amino-4-pentynoic acid, monohydrochloride (1.8 g), NMM (1.5 ml) and a catalytic amount of DMAP in DMF (10 ml) was added. The reaction was stirred overnight at room temperature. Ethyl 3S-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino-4-pentynoate, TFA salt (1.5 g) was isolated by HPLC (RP-CH_3CN/H_2O) as a white solid. MS was consistent with the desired product.

Step B

A solution of the product of Step A (1.5 g) in 1:1 H_2O/CH_3CN (75 ml) was treated with LiOH (pH>12). After 2 hours, the reaction was acidified with TFA and the product was purified by HPLC (RP-CH_3CN/H_2O). The title compound as a lyophilized solid (1.2 g), had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 70

Preparation f 3R-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt



Step A

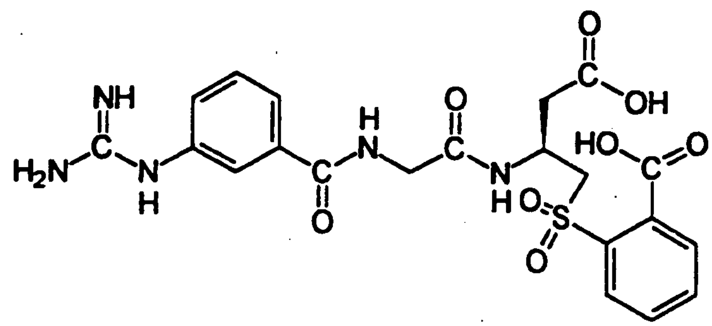
A suspension of m-guanidinohippuric acid HCl (0.8 g) and NMM (0.3 ml) in DMF (2.5 ml) was treated with pivaoyl chloride (0.4 ml). After 30 minutes, a solution of ethyl 3R-amino-4-pentynoate (0.4 g), NMM (0.3 ml) and a catalytic amount of DMAP in DMF (2.5 ml) was added. The reaction was stirred overnight at room temperature. Ethyl 3R-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid trifluoroacetate salt (0.5 g) was isolated by HPLC (RP-CH_3CN/H_2O) as a white solid. MS was consistent with the desired product.

Step B

A solution of the product of Step A (0.5 g) in 1:1 CH_3CN/H_2O (75 ml) was treated with LiOH (pH>12). After 2 hours, the reaction was acidified with TFA and the product was purified by HPLC (RP-CH_3CN/H_2O). The title compound as a lyophilized solid (250 mg), had MS, ^{1}H-NMR and CHN analysis that were consistent with the desired product.

Example 71

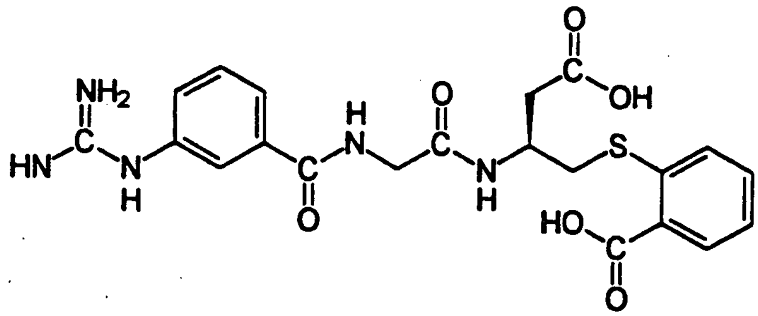
Preparati n of 2-[[2S-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2-(carboxymethyl)ethyl]sulfonyl]benzoic acid, TFA salt



A solution of Example 72 (120 mg) in methanol (10 ml) was treated with m-chlorobenzoic acid (100 mg). The reaction was stirred overnight at room temperature. The product was purified by HPLC (RP-CH_3CN/H_2O). The title compound (100 mg) was isolated as a white solid. MS, ^{1}H-NMR and CHNS analysis were consistent with the desired product.

Example 72

Preparation of 2-[[2S-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2-(carboxymethyl)ethyl]thio]benzoic acid, trifluoroacetate salt



Step A

A solution of Example A (6.2 g) in CH_2Cl_2 (40 ml) at 0°C was treated with triethylamine (4.25 ml) and mesyl chloride (2.3 ml). After 3 hours, phenylmethyl 3S-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[(methylsulfonyl)oxy]butanoate was isolated by extraction using ethyl acetate/diethyl ether. The organic layer was dried using Na_2SO_4 and the excess solvent was removed to give phenylmethyl 3S-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[(methylsulfonyl)oxy]-butanoate (8.8 g). A suspension of the resulting product, K_2CO_3 (3.0 g), and catalytic amounts of 18-crown-6, DMAP and tetrabutylammonium hydrogen sulfate in DMF (10 ml) was treated with methyl thiosalicylate (3.8 ml). After 2 hours the product was extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and the excess solvent was removed under reduced pressure. The resulting oil (10.2 g) was dissolved in CH_2Cl_2 (50 ml) and treated with TFA (20 ml). The reaction was stirred overnight at room temperature. The excess solvent was removed under reduced pressure and the oil was dissolved in 1:1 $CH_3CN:H_2O$ and made basic using NaOH (pH>12). After 2 hours, the reaction

was acidified using TFA and the product was isolated using HPLC (RP-CH_3CN/H_2O). 20% HCl (2 ml) was added and th product was lyophilized. A yellow s lid (0.9 g) was obtained. MS was consistent with 2-[(2-amino-3-carboxypropyl)thio]benzoic acid HCl salt.

Step B

A solution of 3-aminobenzoic acid (41.1 g) in dioxane (300 ml) was treated with 3,5-dimethyl-(pyrazole-1-carboxamidine) HNO_3 (100 g), DIEA (90 ml) and H_2O (100 ml). The reaction was refluxed for 3 hours and stirred overnight at room temperature. The solid was filtered and washed with dioxane (150 ml) and 1:1 dioxane:H_2O (250 ml). The solid was then suspended in diethyl ether (400 ml) and CH_3CN (100 ml) and treated with 4N HCl/dioxane (100 ml) and 20% HCl (1 ml). After 48 hours, the reaction was filtered and dried to give 3-[(aminoiminomethyl)amino]benzoic acid (34.1 g) as a lavender solid. MS was consistent with the desired product.

Step C

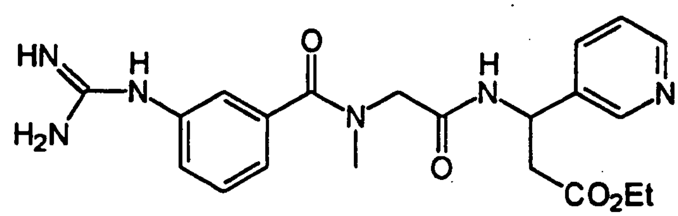
A solution of 2-[(2S-amino-4-carboxybutyl)thio]-benzoic acid (0.9 g) and DIEA (1.5 ml) in DMF (5 ml) was treated with N-[1,1-dimethylethoxy)carbonyl]-glycine, 2,5-dioxopyrrolidin-1-yl ester (1.1 g) and a catalytic amount of DMAP. After 1 hour, methanol (5 ml) and 4N HCl/dioxane (10 ml) were added. After 18 hours, methyl 2-[[2S-[(2-aminoacetyl)amino]-3-(methoxycarbonyl)-propyl]benzoate was isolated by HPLC (RP-CH_3CN/H_2O). The desired product (1.0 g) was obtained as a white solid. MS was consistent with the desired product.

Step D

A solution f the product of Step C (200 mg) and NMM (130 μl) in DMF (1 ml) was treated with of IBCF (152 μl). After 2 minutes, the reaction was treated with a solution of the product of Step B (330 mg), NMM (260 μl) and a catalytic amount of DMAP in DMF (1 ml). After 2 hours, the reaction was treated with H_2O and made basic using NaOH (pH>12). After 4 hours, the reaction was acidified with TFA and the product was isolated by HPLC (RP-CH_3CN/H_2O). The title compound (200 mg) was obtained as a white solid. MS, ^{1}H-NMR and CHNS analysis were consistent with the desired product.

Example 79

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]methylamino]acetyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

To a 200 mL flask equipped with a teflon coated stir bar was added N-t-Boc-sarcosine (3.80 g, 0.019 mole) and dry DMF (70 mL). To this was added N-methyl morpholine, (NMM), (2.1 mL, 1.92 g, 0.019 mole) and the resulting mixture was cooled to 0°C (salt - ice water bath). After several minutes isobutyl-chloroformate, (IBCF), (95%, 2.74 g, 2.6 mL, 0.019 mole) was added. After about five minutes a solution of ethyl 3-amino-3-pyrid-3-yl propionate dihydrochloride salt (5.0 g, 0.019 mole) and NMM (3.84 g, 0.038 mole) in DMF (40 mL) was added and the resulting mixture allowed to react overnight at 0-5°C. The volatiles were removed on a rotary evaporator (60°C) and a semi-solid was obtained. This was taken up in ethyl acetate and dilute hydrochloric acid, pH 2. To the aqueous layer was added EtOAc (200 mL) and the pH of the aqueous layer was brought to about 7 by the addition of solid sodium bicarbonate. The pH was adjusted to 8 by the addition of dilute aqueous NaOH. The layers were separated and the aqueous layer washed with EtOAc. The combined organic layers were dried (Na_2SO_4) and volatiles removed to giv a thick oil whose MS was consistent with the desired product.

Step B

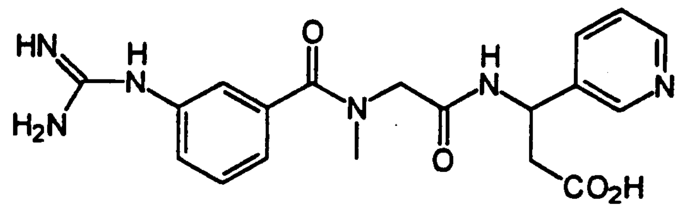
Th product from Step A was dissolved in dioxan (20 mL) and transferred to a round-bott m flask equipped with a teflon-covered stir bar and connected to a mineral oil bubbler. To this was added 4 N HCl in dioxane (about 30 mL). After about one hour a vacuum was applied to remove excess HCl gas and the reaction mixture was concentrated on a rotovap. Excess HCl was chased with a second evaporation from dioxane to obtain a white foam. The MS and NMR were consistent with the desired product as a dihydrochloride salt.

Step C

The title compound was obtained by coupling 3-guanidinobenzoic acid with the product of Step B using substantially the same conditions and procedure as employed in Step A. Thus, to 3-guanidinobenzoic acid hydrochloride (1.5 g, 7.0 mmole, Aldrich) dissolved in DMF (70 mL) was added an equivalent of NMM (0.77 mL, 7.0 mmole) and the mixture cooled to 0°C. To this was added one equivalent of IBCF (0.91 mL, 7 mmole) and after several minutes a solution of 1.1 equivalent of the sarcosine pyridyl amino acid ester prepared in Step B (2.4 g of di HCl salt) and NMM (0.78 mL) in DMF (about 50 mL) was added and the reaction mixture allowed to warm to room temperature overnight. Volatiles were removed and the product isolated by preparative reverse phase high performance liquid chromatography (RPHPLC) using a gradient of 99:1 water, 0.05% TFA: acetonitrile, 0.05% TFA to 45:55 over 60 minutes at 80 mL/min flow rate. The desired product fractions were combined and lyophilized to give the title compound (0.96 g) as a fluffy solid whose NMR and MS were consistent with the desired product.

Exampl 80

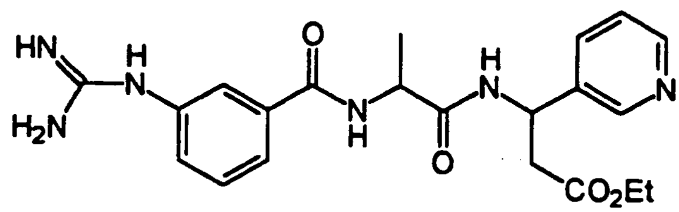
Pr paration of (±)β-[[2-[[[3-[(aminoimin methyl)amino]-phenyl]carbonyl]methylamino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



The product obtained in Example 79 (0.33 g) was dissolved in water (20 mL) and the pH adjusted to 11 by the addition of dilute aqueous LiOH. After about one hour the ester was substantially hydrolyzed as indicated by analytical C-18 HPLC. The desired product (±)β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-carbonyl]methylamino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt was isolated by preparative C-18 HPLC using substantially the same conditions outlined in Example 79, Step C, and lyophilized (0.19 g). Proton NMR, FAB MS, and elemental analysis (CHN) were consistent with the desired product.

Example 81

Preparation of ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]-1-oxopropyl]amino]-pyridine-3-propanoate, bis(trifluoroacetate) salt



Step A

R,S-N-t-Boc alanine (2.0 g, 0.0106 mole) was coupled to ethyl 3-amino-3-pyridyl-propionate dihydrochloride (3.2g). Using the procedure of Example 79, Step A. The product obtained (3.42 g, 88% isolated yield) had MS and NMR consistent with the desired N-Boc product.

Step B

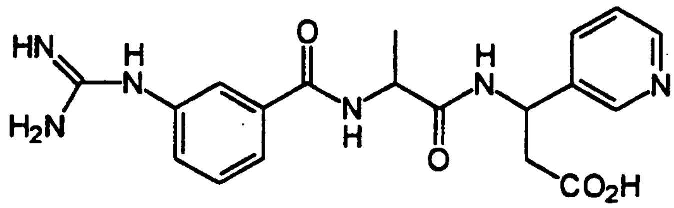
The Boc protecting group was removed from the product of Step A using the procedure of Example 79, Step B to obtain the dihydrochloride salt (3.5 g) as a white solid whose MS and NMR spectrum were consistent with the desired amino acid ester.

Step C

Preparation of ethyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-1-oxopropyl]amino]pyridine-3-propanoate, bis(trifluoroacetate) salt. The amino acid ester (1.6 g) obtained in Step B was coupled to 3-guanidinobenzoic acid (0.75 g, 3.5 mmole) using the conditions of Example 79, Step C to obtain the title compound (1.8g , 2.7 mmole , 79% isolated yield) bis trifluoroacetate salt as a white solid after ly philization. MS and pr ton NMR were consistent with the desired product.

Example 82

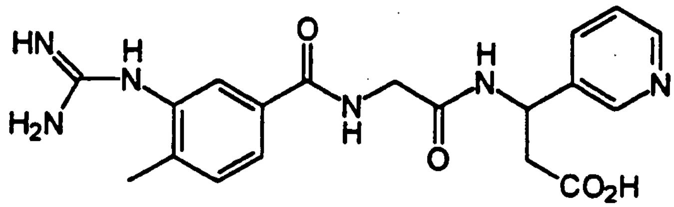
Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]-1-oxopropyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



The product of Example 81 (0.5 g) was hydrolyzed to the acid using the procedure of Example 80. The desired product as the di-TFA salt was isolated by preparative C-18 HPLC using substantially the same conditions outlined in Example 79, Step C, and lyophilized (0.45 g). Proton NMR and FAB MS were consistent with desired product.

Example 83

Preparation of (±) β-[[2-[[[3-[(amin iminomethyl)-amino]-4-methylphenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



Step A

N-t-Boc glycine was coupled to 3-amino-3-(3-pyridyl) propionic acid dihydrochloride (5.0 g, 0.019 mole) using the procedure of Example 79, Step A to obtain, after work-up, a yellow oil (6.0 g, 90%) whose MS was consistent with the desired compound.

Step B

The Boc protecting group was removed by dissolving the product of Step A (5.9 g) in dioxane (about 20 mL) and TFA and the reaction was allowed to proceed for several minutes until the evolution of gas ceased. The volatiles were removed on a rotavap to obtain a brown oil. MS and NMR were consistent with the desired product.

Step C

The amino-ester prepared in Step B was coupled to 4-methyl-3-nitrobenzoic acid using the procedure of Example 79, Step C to obtain an oil that was purified by preparative RPHPLC (C-18) to obtain the desired coupled product (1.76 g) as an amorphous solid whose NMR and MS were consistent with the desired product.

Step D

The nitro group present in the product from Step C was reduced to the aniline using th following procedure. The product from Step C (1.75 g) was transferred to a 6 oz. Fischer-Porter pressure bottle equipped with a pressure gauge and inlet and outlet valves. The starting compound was dissolved in glacial acetic acid, 3% Pd on carbon catalyst (about 1 g) was added and the vessel sealed. After three vacuum-nitrogen cycles the vessel was pressurized with hydrogen (55 psig) and the reaction was allowed to proceed overnight at room temperature. The catalyst was removed by filtering through celite and the colorless solution concentrated to give a yellow, viscous oil (2.0 g) whose MS was consistent with the desired aniline.

Step E

The aniline (1.0 g, 2.12 mmole) from Step D was guanylated using the following procedure. The aniline was dissolved in acetonitrile (about 50 mL) and 1H-pyrazole-1-carboxamidine hydrochloride (0.342 g, 2.3 mmole) added in water along with triethylamine (0.64 g, 0.92 mL, 6.4 mmole) and the solution brought to reflux. After heating overnight the volatiles were removed on the rotovap and the semi-solid obtained purified by preparative RPHPLC to obtain the desired guanidated product (0.3 g after lyophilization) whose NMR and MS were consistent with the desired structure.

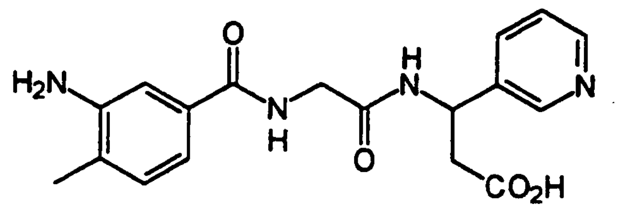
Step F

The guanidino-ester obtained in Step E was hydrolyzed to the acid by dissolving the ester (0.3 g) in water (20 mL) and the pH brought to 11 by the addition of dilute LiOH. After about an hour complet conversion to th acid was observed by analytical RPHPLC and the title compound, purified by preparative

HPLC and lyophilized to obtain th di-TFA salt as a whit powder (0.19 g) whose NMR and MS were consistent with the desired product.

Example 84

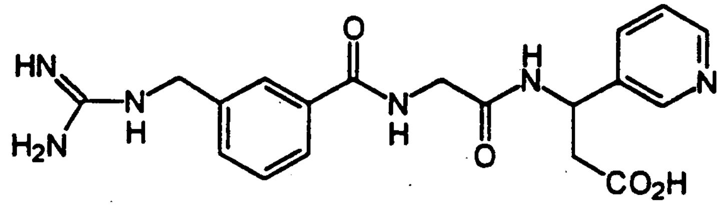
Preparation of β-[[2-[[(3-amino-4-methylphenyl)-carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, bis(trifluoroacetate) salt



The aniline-ester obtained in Example 83, Step D was hydrolyzed to the acid using conditions similar and purification scheme similar to Example 83, Step F to obtain the desired aniline-acid, β-[[2-[[(3-amino-4-methylphenyl)carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, as the di-trifluoroacetate salt whose NMR and MS were consistent with the desired product.

Example 85

Preparation of (±) β-[[2-[[[3-[[(aminoimin methyl)-amino]methyl]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, bis(trifluoroacetate) salt



Step A

3-Cyanobenzoic acid (7.0 g, 0.0476 mole) was added to a round-bottom flask (200 mL) and dissolved in DMF:pyridine (50 mL). To this solution was added disuccinylcarbonate (DSC, 14.6 g, 0.0571 mole) and a catalytic amount of DMAP. Upon cessation of gas evolution, glycine t-butyl ester (9.6 g, 0.057 mole) was added and allowed to react overnight. Triethylamine (10 mL) was added and stirred for several minutes. Volatiles were removed on a rotovap and worked up by dissolving the crude reaction mixture in water and ethyl acetate. The aqueous layer was made acidic by addition of dilute hydrochloric acid, the layers separated, and the water layer discarded. The organic layer was washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated to obtain a product (11.1 g) whose MS was consistent with the desired, coupled product.

Step B

The cyano-t-butyl ester obtained in Step A was reduced to the corresponding benzylamine compound in similar fashion to Example 82, St p D. Thus, cyano-t-butyl ester (10.0 g, 0.0681 mole) was dissolved in acetic acid (about 70 mL) with heating and c oled.

Catalyst was added (0.5 g 3% Pd on carbon) and the reaction transferred to a 6 oz Fisch r-Porter bottle and pressurized with hydrogen (55 psig). Hydrogen was continually added until hydrogen uptake ceased. The catalyst was removed by filtration through celite and the solvent was removed by evaporation to obtain crude benzyl amino t-butyl ester whose MS was consistent with the desired compound.

Step C

The Boc group was removed from the product of Step B in a fashion similar to Example 83, Step B to obtain the benzyl amino acid whose MS was consistent with the desired product.

Step D

The amino acid (9.0 g, 0.03 mole) obtained in Step C was dissolved in acetonitrile:water (about 1:1) and excess triethylamine added. After several minutes volatiles were removed and crude triethylamine salt obtained. This was re-dissolved in acetonitrile:water (200 mL) and 1H-pyrazine-1-carboxamidine hydrochloride (4.3 g, 0.03 mole) was added and the reaction mixture brought to reflux. After allowing the reaction to reflux overnight the reaction was concentrated to a semisolid. This was dissolved in water (20 mL) and the pH was adjusted to about 7 by addition of solid sodium bicarbonate. A precipitate formed and was removed by filtration. The MS and NMR were consistent with the zwitter-ion. This product was converted to the hydrochloride salt by treating the zwitter-ion with water and adding hydrochloric acid until the pH was about 2. This was lyophilized to obtain the hydrochloride salt.

Step E

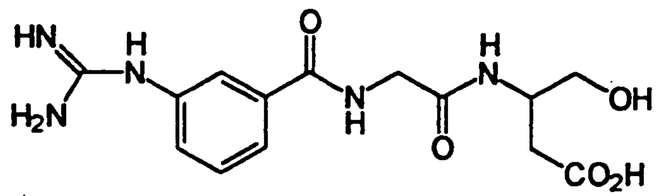
The guanidino-acid was obtained by hydrolyzing th product btained in Step D (0.47 g) using the procedure of Example 83, Step F. Upon lyophilization a solid is obtained (0.41 g) as the di-TFA salt whose NMR and MS were consistent with the desired product.

Step F

The guanidino-acid prepared in Step E was coupled to 3-amino-3-(3-pyridyl) propionic acid using the procedure of Step A. Preparative RPHPLC was employed to obtain a solid (1.66 g) whose NMR and MS were consistent with the desired product.

Example 86

Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-hydroxybutanoic acid



Step A

Preparation of 3-N-t-Boc-amino-4-hydroxy-butyric acid benzyl ester.

N-t-Boc aspartic acid, alpha-benzyl ester (10.0 mmol) was dissolved in THF (10 mL) and added dropwise over a period of 30 minutes to a 0°C solution of BH_3-THF (20 mL, 20.0 mmol), under N_2. After the mixture was stirred for an additional 1-2 hours at 0°C, the reaction was quenched with a solution of 10% AcOH in MeOH (10 mL), and the solvent evaporated. The residue was dissolved in EtOAc and extracted with 1N HCl, H_2O, and 1 M NH_4HCO_3. After being dried over $MgSO_4$, the product was recovered by removal of the solvent in vacuo. MS was consistent with the desired product.

Step B

Preparation of N-t-Boc-3-amino-2,3-dihydro-5-oxo-3S-furan.

The 3-N-t-Boc-amino-4-hydroxy-butyric acid benzyl ester (20 g, 64 mmol) was stirred in dichloromethane (200 mL) at 25°C for 16 hours in the presence of a catalytic amount of camphor sulfonic acid. The solvent was removed *in vacuo*. Th crud material was purified by flash chromatography on a bed of silica gel (22 cm x 6 cm of Merck 60 Silicag 1) eluted with a gradi nt of hexane/ethyl acetat (90/10 to 70/30; 200 mL/min flow

rate). The pure N-t-Boc-3-aminolactone was isolated as a white solid (5.4 g) wh se MS was c nsistent with the desired compound.

Step C

Preparation of 3-amino-2,3-dihydro-5-oxo-3S-furan hydrochloride.

The 3-N-t-Boc amino lactone (5.0 g, 25 mmol) isolated in Step B was dissolved in 4N HCl dioxane (20 mL). After stirring 45 minutes at 25°C, 4N HCl dioxane solution (10 mL) was added and after 1 hour at 25°C, the excess HCl was removed *in vacuo*. The resulting solution deposited crystals upon standing. The white crystalline material was filtered and dried (2.9 g) ; ^{1}H NMR (DMSO $-d_6$) δ 2.55 (dd, 1H, J1 = 18.3 Hz, J2 = 2.5 Hz), 3.0 (dd, 1H, J1 = 8.5 Hz, J2 = 18.3 Hz), 4.1 (m, 1H), 4.35 (dd, 1H, J1 = 10.5 Hz, J2 = 2.7 Hz), 4.5 (dd, 1H, J1 = 10.5 Hz, J2 = 6.5 Hz), MS (FAB) 102.1(M+H+).

Step D

3-amino-2,3-dihydro-5-oxo-3S-furan hydrochloride was coupled to *meta*-guanidino-hippuric acid hydrochloride (GIHA) using the following procedure. To GIHA (1.6 g, 5.9 mmole) in DMF (about 30 mLs) was added an equivalent of NMM (0.59 g, 0.64 mL, 5.82 mmole) and the mixture allowed to stir for several minutes until a precipitate formed. The mixture was cooled to 0°C and an equivalent of DSC (1.49 g, 5.82 mmole) and a catalytic amount of DMAP were added and the reaction allowed to proceed for at least 0.5 hour. Upon substantially complete activation 3-amino-5-oxo-3S-furan hydrochloride (0.8 g, 5.82 mmole) was added to the reaction mixture followed by an equivalent of NMM (0.59 g, 0.64 mL, 5.82 mmole) and the reaction allowed to proceed to completion (1-16 hours). The volatiles w re removed (vacuum rotary evaporation at 60°C) and the residue dissolved in a minimum am unt of

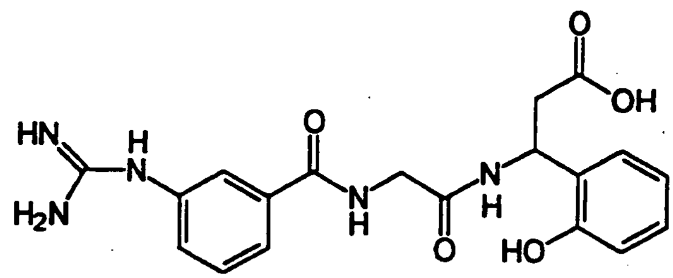
water:acetonitrile (using the minimum amount of acetonitrile to effect solution). The solution was brought t pH of about 3 by addition of neat TFA and isolation of desired coupled product was achieved by preparative RPHPLC to obtain the mono TFA salt as a hygroscopic solid after lyophilization (0.54 g).

Step E

The title compound was obtained by dissolving the product from Step D (0.54 g) in water (20 mL). The pH of the solution was brought to about 11 by addition of dilute aqueous NaOH. Upon completion of the reaction, as determined by analytical RPHPLC, the solution (final pH about 8) was lyophilized. The product's identity was confirmed by proton NMR and MS.

Example 87

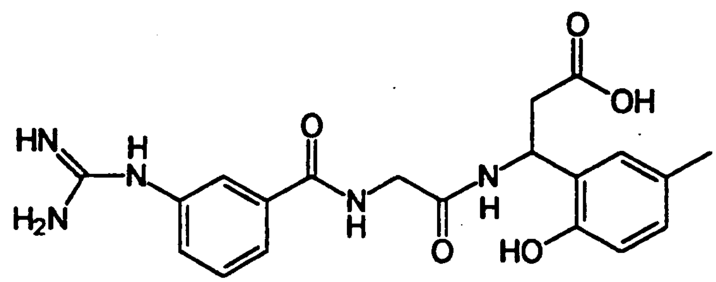
Preparation of (±) sodium β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-amino]-2-hydroxybenzenepropanoate, sodium salt, trifluoroacetate salt



3-Amino-hydrocoumarin hydrochloride (2.0 g, 0.010 mole), prepared according to J. Rico, Tett. Let., 1994, 35, 6599-6602, was coupled to GIHA (1.50 g, 0.0041 mole) using substantially the procedure of Example 86, Step D. Purification by preparative RPHPLC gave the desired product as a mixture of coumarin and hydroxy-acid TFA salts as a light yellow powder after lyophilization (1.50 g). Essentially complete conversion to the desired phenol-acid was obtained by dissolving the purified mixture in water, adjusting the pH to 7-8 with dilute aqueous NaOH, and lyophilizing. MS and proton NMR were consistent with the phenol-acid (carboxylate) form of the molecule (as the trifluoroacetate, sodium salt).

Example 88

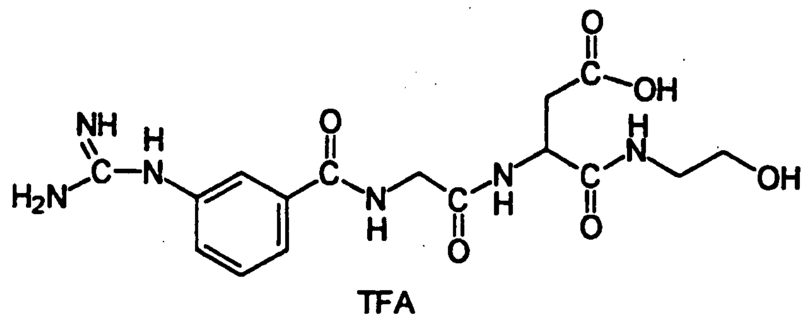
Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2-hydroxy-5-methylbenzenepropanoic acid, trifluoroacetate salt



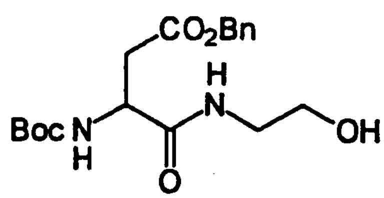
3-Amino-6-methylhydrocoumarin, prepared according to the reference cited in Example 87, was coupled to GIHA using amounts, conditions, and purification similar to Example 87 to obtain a tan solid (0.76 g) whose NMR and MS were consistent with the desired product (as the TFA, sodium salt).

Example 89

Preparation f (±) 3-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-[(2-hydroxyethyl)amino]-4-oxobutanoic acid, trifluoroacetate salt

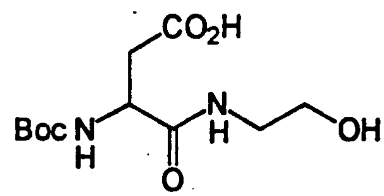


Step A



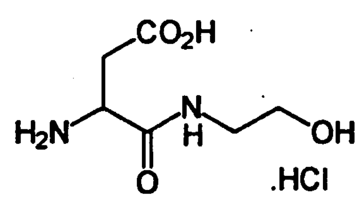
N-t-Boc aspartic acid, alpha-benzyl ester (7.7 mmol, 2.50 g) was dissolved in DMF: pyridine (1:1, 70 mL) and DSC (8.5 mmol, 2.2 g) was added together with a catalytic amount of DMAP. After cessation of gas evolution (about 1 hour), ethanol amine (0.52 g, 8.3 mmol) in pyridine (20 mL) was added and allowed to react at room temperature overnight. Volatiles were removed to obtain a golden oil. The resulting product was partitioned between EtOAc and aqueous HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution, water, dried (anhydrous sodium sulfate) and volatiles removed to obtain a golden oil (2.64 g) whose proton NMR and mass spectra correspond to the desired protected amide.

Step B



The crude product from Step A (2.3 g) was de-benzylated using standard procedures. Thus, the product from Step A was taken up in acetic acid (about 70 mL) transferred to a Fischer-Porter pressure bottle and 3% palladium on carbon (1 g) and hydrogen added (54 psig). The reaction was vigorously stirred and hydrogen replenished as needed. After no further hydrogen uptake (about 1 hour) the catalyst was removed by filtration through a celite pad and volatiles removed to obtain a colorless oil (1.73 g). Proton NMR and MS were consistent with the desired de-benzylated product.

Step C



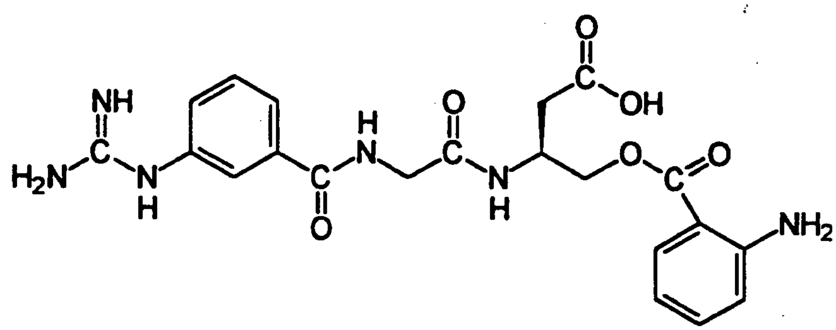
The crude product obtained in Step B was dissolved in dioxane (20 mL) and to this was added 4N HCl in dioxane (40 mL) with vigorous stirring. The reaction was allowed to proceed until gas evolution ceased (about 15 minutes). The volatiles were removed and a golden oil was obtained which was triturated with diethyl ether. Proton NMR and mass spectra were consistent with the desired N-deprotected, amino acid product.

Step D

The product of Step C (1.0 gm, 4.7 mmol) was coupled to GIHA (1.5 g, 4.11 mm 1) using a procedure similar to that of Example 86, Step D. The crude coupling reaction was concentrated to a thick oil and reconstituted in water:acetonitrile, and purified by preparative RPHPLC to obtain the desired (±) 3-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]amino]-acetyl]amino]-4-[(2-hydroxyethyl)amino]-4-oxobutanoic acid, trifluoroacetate salt (0.44 g after lyophilization). Proton NMR and mass spectra were consistent with the desired product.

Example 94

Preparation of 2S-[[2-[[[3-[[aminoiminomethyl]-amino]phenyl]carbonyl]amino]acetyl]amino]-3-carboxypropyl 2-aminobenzoate, bis(trifluoroacetate) salt, monohydrate



Step A

Preparation of Benzyl-3-N-tBoc-amino-4-hydroxy-(3S)-butyrate

N-tBoc-L-aspartic acid, β-benzyl ester (Sigma) (75 g, 20 mmol) was dissolved in THF (30 ml) and added dropwise over a period of 30 minutes to BH_3-THF (400 ml, 40 mmol) at 0°C under a N_2 atmosphere. After the solution was stirred for 2.5 hours at 0°C, the reaction was quenched with 50 ml solution of 10% acetic acid in MeOH, and the solvent was evaporated. The residue was dissolved in ether (200 ml) and washed with 1N HCl, saturated K_2CO_3, water and dried over $MgSO_4$. The product was isolated by removal of the solvent *in vacuo* (mp 56-57°C from isopropyl ether/hexane). ^{1}H-NMR (d_6-DMSO) δ 1.4 (s, 9H), 2.68 (d, 2H, J = 6 Hz), 3.82 (d, 2H, J = 5 Hz), 4.01 (m, 1H), 5.16 (s, 2H), 5.21 (bs, 1H), 7.37 (bs, 5H).

Step B

Preparation of b nzyl-3-amin -4-(anthranilate)-(3S)-butyrate

Benzyl-3-N-tBoc-amino-4-hydroxy-(3S)-butyrate (10 g, 32 mmol) was dissolved in 50 ml of dimethylformamide followed by triethylamine (4.4 g, 46 mmol). Isatoic anhydride (5.0 g, 3 mmol) was added and the solution was stirred for 24 hours at 25°C. After the reaction (monitored by reverse phase HPLC) was complete, water was added and the product extracted with ethyl acetate (100 mL) and dried over Na_2SO_4. Solvent evaporation resulted in 12 g of a yellow oil. To this oil, dioxane (20 mL) was added followed by 4N HCl in dioxane (20 mL). The reaction was left to proceed for 4 hours, ether was added and an oily mass separated from the solution. Ether was again added to the oily mass and decanted. This procedure was repeated two times. Ether was added to the semi solid and stirred vigorously for 16 hours. A white solid was collected having MS and ^{1}H-NMR consistent with the proposed structure.

Step C

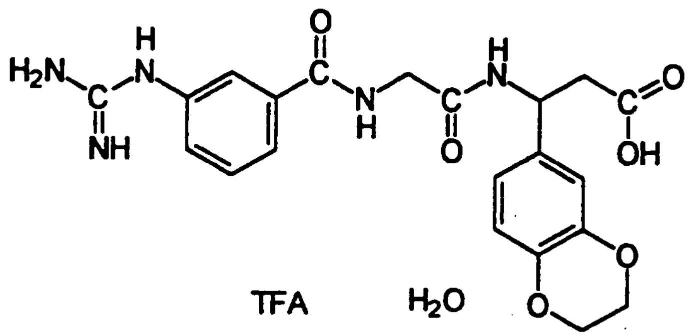
N,N'-Disuccinimidylcarbonate (DSC) (1.4 g, 0.5 mmol) was added to GIHA (1.0 g, 0.5 mmol) in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour benzyl-3-amino-4-anthranilate-(3S)-butyrate (0.7 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) was added in one portion. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.0 g). MS, and ^{1}H-NMR were consistent with proposed structure.

St p D

The benzyl ester from Step C was hydrogenated using H_2 gas and catalytic Pd/C (500 mg, 5%) for 4 hours. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.0 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 95

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-1,4-benzodioxin-6-propanoic acid, trifluoroacetate salt



Step A

To 1,4-benzodioxan-6-carboxaldehyde (Aldrich)(10 g) in isopropanol (205 mL) was added ammonium acetate (12.5 g) followed by malonic acid (6.0 g). The reaction mixture was stirred at reflux for 5 hours. The reaction mixture was filtered hot and washed with hot isopropanol (100 mL). The resulting white solid was dried to give DL-3-amino-3-(1,4-benzodioxane) propionic acid (6.3 g) as a white solid. MS, and ^{1}H-NMR were consistent with the proposed structure.

Step B

DL-3-amino-3-(1,4-benzodioxane)propionic acid (6 g) from Step A was slurried in absolute EtOH (250 mL) and acetyl chloride (20 mL). The slurry was then heated at reflux for 4 hours. The reaction mixture was cooled to 25°C and the solvent evaporated under reduced pressure to give a solid which was washed with ethyl ether (50 mL) to give DL-ethyl-3-amino-3-(1,4-benzodioxane)propionate (6.5 g) as a white solid. MS and ^{1}H-NMR were consistent with propos d structure.

Step C

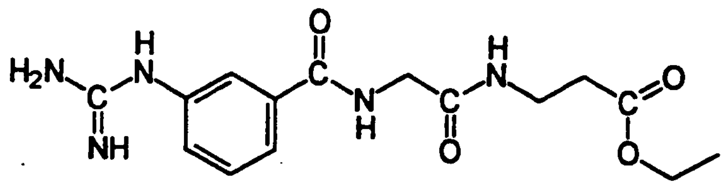
N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mm 1) was added to GIHA (1.0 g, 0.5 mmol) in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour the product from Step B (0.7 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) was added in one portion. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step D

DL-ethyl-3-amino-3-(1,4-benzodioxane)propionate adduct (the product from Step C) (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 96

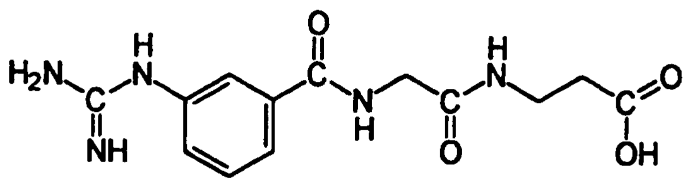
Preparation of N-[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]-β-alanine, ethyl ester



N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added to GIHA (1.0 g, 0.5 mmol) in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour beta-alanine ethyl ester hydrochloride (0.7 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) was added in one portion. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 1.1 mg of a white solid. MS and ^{1}H-NMR were consistent with proposed structure.

Example 97

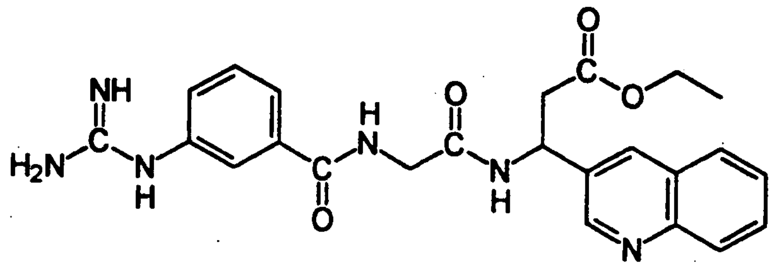
Preparation of N-[2-[[[3-[(aminoiminomethyl)amin]-phenyl]carbonyl]amino]acetyl]-β-alanine



The compound of Example 96 (500 mg) was dissolved in water/acetonitrile (1:1) followed by the addition of lithium hydroxide (200 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) triflouroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 375 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 98

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-quinoline-3-propanoate, bis(trifluoroacetate) salt



2TFA H_2O

Step A

To 3-quinolinecarboxaldehyde (Aldrich) (10 g) in isopropanol (205 mL) was added ammonium acetate (12.5 g) followed by malonic acid (6 g). The reaction mixture was stirred at reflux for 5 hours. The reaction mixture was filtered hot and washed with hot isopropanol (100 mL). The resulting white solid was dried to give DL-3-amino-3-(3-quinoline)propionic acid (6.3 g) as a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Step B

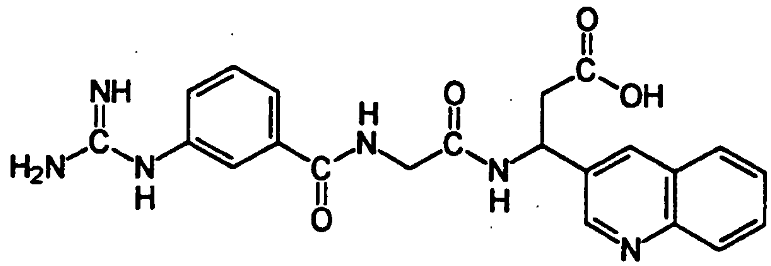
DL-3-amino-3-(3-quinoline)propionic acid (6 g) from Step A was slurried in absolute EtOH (250 mL) and acetyl chloride (20 mL). The slurry was then heated at reflux for 4 hours. The reaction mixture was cooled to 25°C and the solvent evaporated under reduced pressure to give a solid which was washed with ethyl ether (50 mL) to give DL-ethyl-3-amino-3-(3-quinoline)propionate (6.5 g) as a white solid. MS and ^{1}H-NMR were consistent with the pr posed structure.

Step C

To N,N'-disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added GIHA (1.0 g, 0.5 mmol) in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour ethyl DL-3-amino-3-(3-quinoline)propionate (1.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) was added in one portion. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.2 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 99

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]quinoline-3-propanoic acid, bis(trifluoroacetate) salt

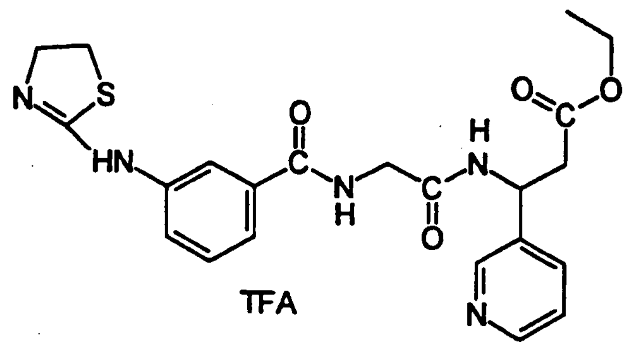


2TFA H_2O

The compound from Example 98 (600 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C and monitored by HPLC. After complete hydrolysis (1-2 hours) triflouroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 470 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

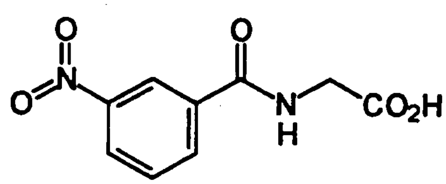
Example 100

Preparation of ethyl β-[[2-[[[3-[(4,5-dihydrothiazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, trifluoroacetate salt



Step A

Preparation of 3-Nitrobenzoyl Glycine:



Glycine (20 g, 266 mmol) was added to water (200 mL), followed by potassium hydroxide (20 g, 357 mmol) and cooled to 0°C in an ice bath. To this solution 3-nitrobenzoyl chloride (Aldrich) (20 g, 108 mmol) was added in a solution in acetonitrile (20 mL) drop-wise over a 10 minute period. After complete reaction (3-4 hours) concentrated hydrochloric acid was added until pH = 1 followed by saturated aqueous NaCl (75 mL). The product was filtered, washed with water and air dried (22 g, 90% yield). ^{1}H-NMR (d_6-DMSO) δ, 3.92 (d, 2H, J = 6.1), 7.9 (t, 1H, J = 7.9), 8.3 (t, 1H, J = 5.6), 8.35 (m, 2H), 8.69 (s, 1H), 9.25 (t, 1H, J = 7.2 Hz). MS (FAB) m/e 231.0 (M+Li+).

Elemental Analysis for $C_9H_8N_2O_5$

Calc'd:	C, 45.89; H, 4.25; N, 9.92
Found:	C, 45.97; H, 4.44; N, 10.11

Step B

3-nitrobenzoyl glycine, prepared in Step A above (4 g) was dissolved in ethan 1 (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*.

Step C

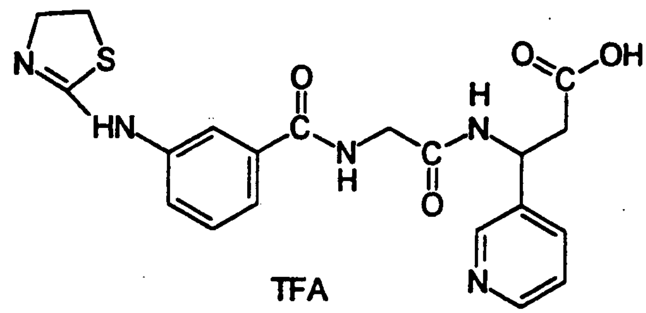
Acetonitrile (5 mL) was added to the crude aniline from Step B followed by 2-(methylthio)-2-thiazoline (7 g) and heated to reflux for 6 hours. The solvent was removed under reduced pressure to give a solid. Diethyl ether was added and the solid was filtered to give a tan colored solid (4.6 g).

Step D

N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added to 2-(methylthio)-2-thiazoline (1.0 g, 0.5 mmol) in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour ethyl DL-3-amino-3-(3-pyridyl)propionate (1.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) was added in one portion. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (520 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 101

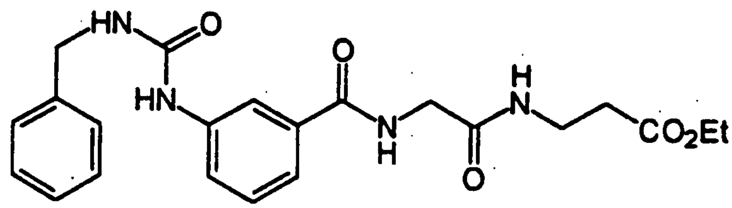
Preparati n of β-[[2-[[[3-[(4,5-dihydrothiazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt



The compound of Example 100 (600 mg) was dissolved in water/acetonitrile (1:1) followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) triflouroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 470 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 102

Preparation of N-[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]-β-alanine, ethyl ester



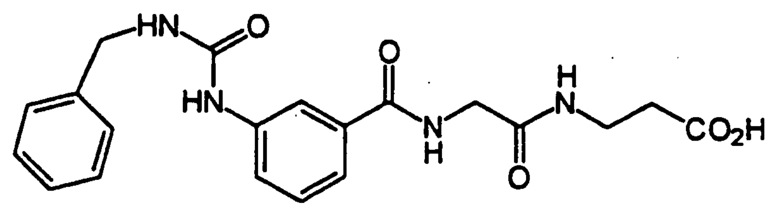
Ethyl (3-nitrobenzoylglycyl)-3-amido propionate (2 g, 0.62 mmol) (Example 100, Step A) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzyl isocyanate (700 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the solid was filtered to give the benzyl urea as a salmon colored solid (2.6 g, 99% yield). The product (1 g portion) was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid: ^{1}H NMR (d_6-DMSO) δ, 1.17 (t, 3H, J = 7.3 Hz), 2.48 (t, 2H, J = 7.1 Hz), 3.45 (q, 2H, J_1 = 6.8 Hz, J_2 = 13.2 Hz), 3.80 (d, 2H, J = 6.9 Hz), 4.06 (q, 2H, J_1 = 7.5 Hz, J_2 = 13.4 Hz), 4.31 (d, 2H, J = 7.5 Hz), 7.2-7.4 (m, 5H), 7.8 (t, 1H, J = 8.0 Hz), 7.85 (bs, 1H), 8.1 (t, 1H, J = 5.6 Hz), 8.35 (m, 2H), 8.71 (s, 1H), 8.78 (bs, 1H), 9.22 (bs, 1H).
MS (FAB) m/e 427.3 (M+H+).

Elemental Analysis

$C_{22}H_{26}N_4O_5$ 1.5 H_2O	Calc'd.:	C, 58.28 H, 5.74 N, 12.36
	Found:	C, 58.48 H, 5.57 N, 12.25

Example 103

Preparation of 3-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-propanoic acid



The compound of Example 102 (400 mg, 0.094 mmol) was dissolved in water/acetonitrile (1:1), followed by addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 265 mg of a white solid: ^1H NMR (d_6-DMSO) δ, 2.48 (t, 2H, J = 7.1 Hz), 3.45 (q, 2H, J_1 = 6.8 Hz, J_2 = 13.2 Hz), 3.80 (d, 2H, J = 6.9 Hz), 4.31 (d, 2H, J = 7.5 Hz), 7.2-7.4 (m, 5H), 7.8 (t, 1H, J = 8.0 Hz), 7.85 (bs, 1H), 8.1 (t, 1H, J = 5.6 Hz), 8.35 (m, 2H), 8.71 (s, 1H), 8.78 (bs, 1H), 9.22 (bs, 1H).

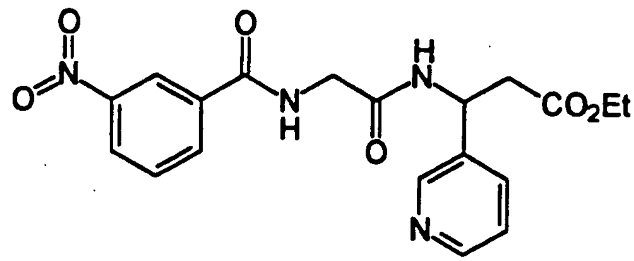
MS (FAB) m/e 405.6 (M+Li+).

Elemental Analysis

$C_{20}H_{22}N_4O_5$ 0.5H_2O	Calc'd.:	C, 59.00	H, 5.39	N, 13.75
	Found:	C, 59.29	H, 5.11	N, 13.63

Example 104

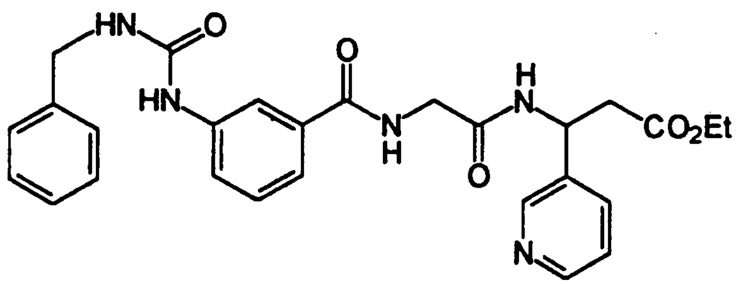
Preparation f ethyl β-[[2-[[(3-nitrophenyl)-carbonyl]amin]acetyl]amino]pyridine-3-propanoat



The same procedure used in the preparation of Example C was followed substituting an equivalent amount of DL-ethyl 3-amino-3-pyridyl propionate for ethyl beta-alanine hydrochloride. N,N'-Disuccinimidyl carbonate (14 g, 5.5 mmol) was added to 3-nitro-benzoyl glycine (10 g, 4.5 mmol) in dry dimethylformamide (30 mL) followed by dimethylaminopyridine (200 mg). After a period of 1 hour DL-ethyl 3-amino-3-(3-pyridyl) propionate dihydrochloride (13 g, 4.6 mmol) in 20% aqueous potassium carbonate (50 mL) was added in one portion. After complete reaction the product was collected by filtration (11.5 g, 80% yield). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 105

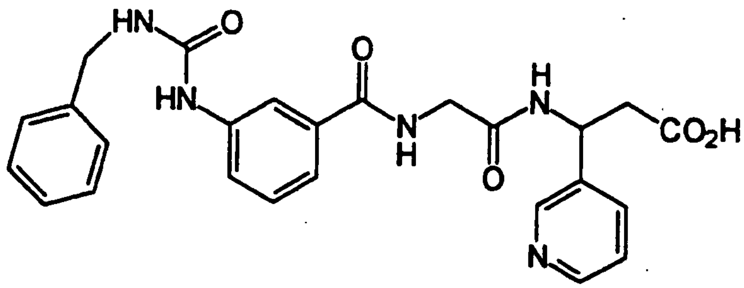
Preparation of ethyl β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoate, trifluoroacetate salt



DL-Ethyl(3-nitrobenzoyl glycyl)-3-amido-3-pyridyl propionate (2 g, 0.62 mmol) of Example 104 was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzyl isocyanate (700 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product was filtered. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.5 g). MS and NMR were consistent with the proposed structure.

Example 106

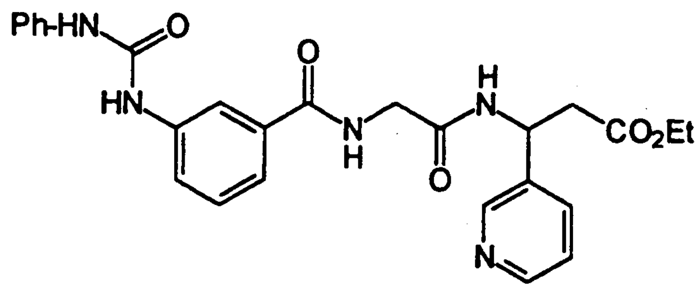
Preparation f (±) β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid



The compound of Example 105 (400 mg, 0.094 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (200 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 107

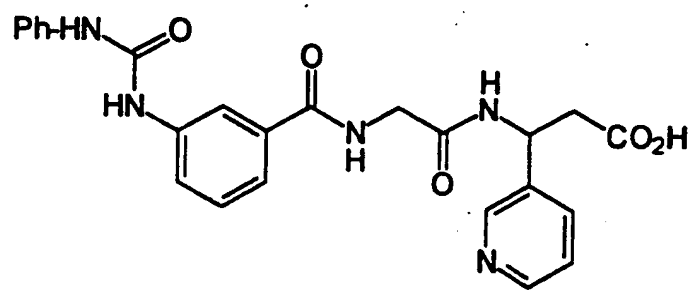
Preparation of ethyl β-[[2-[[[3-[[(phenylamin)-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoate



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-(3-pyridyl)propionate (2 g, 0.64 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by phenyl isocyanate (600 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product was filtered. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 108

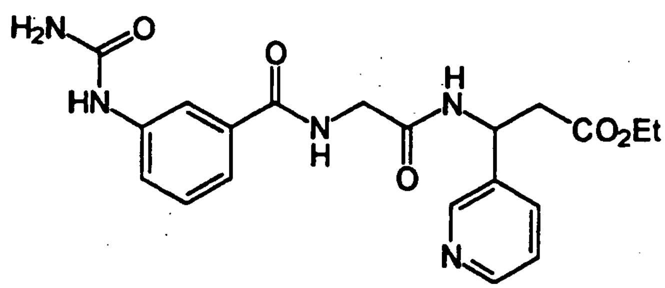
Preparation of β-[[2-[[[3-[[(phenylamino)-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amin]-pyridine-3-propanoic acid, trifluoroacetate salt



The compound of Example 107 (500 mg, 0.095 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (350 mg). MS and ^{1}H-NMR were consistent with proposed structure.

Example 109

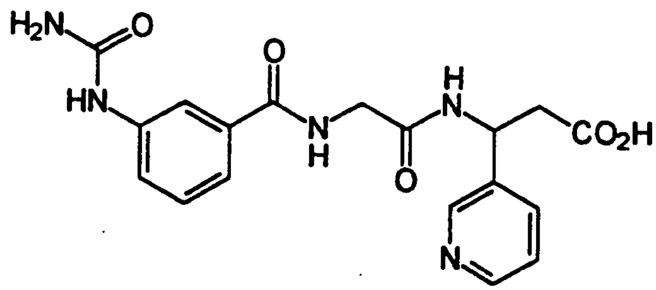
Preparation f ethyl β-[[2-[[[3-(aminocarbonylamino)-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, trifluoroacetate salt



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-(3-pyridyl)propionate (2 g, 0.62 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Hydrochloric acid (20%, 75 mL) was added to the crude aniline followed by urea (2 g). The solution was heated to reflux for 15 hours. After complete reaction (15 hours), the product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.2 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 110

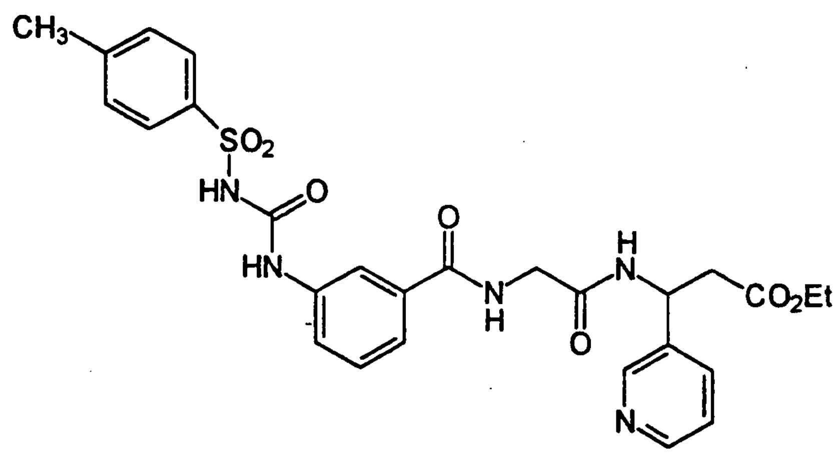
Preparation f β-[[2-[[[3-(aminocarbonylamino)-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt



The compound of Example 109 (500 mg, 0.095 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (350 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 111

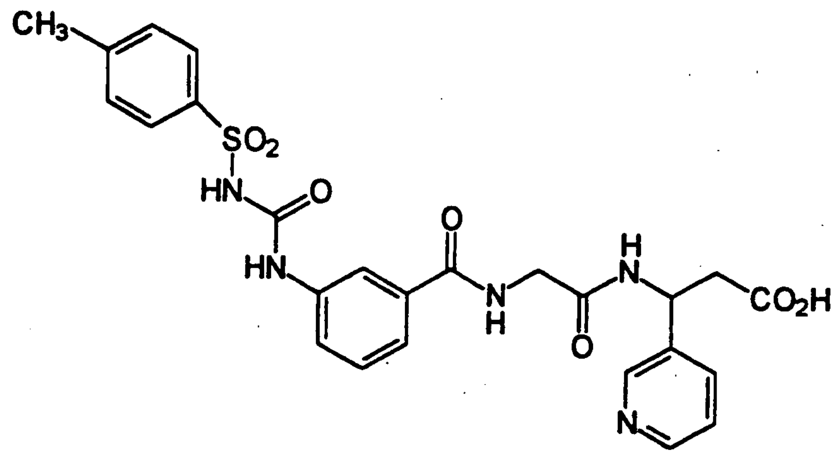
Preparation of ethyl β-[[2-[[[3-[[[[(4-methylphenyl)-sulfonyl]amino]carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoate, trifluoroacetate salt



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-(3-pyridyl)propionate (2 g, 0.64 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by p-toluensulfonyl isocyanate (600 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product was filtered. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.1 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 112

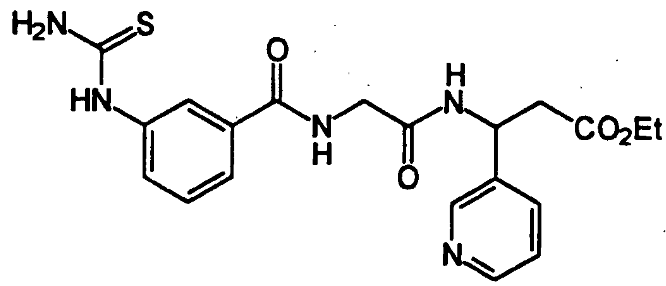
Preparation of β-[[2-[[[3-[[[[(4-methylphenyl)-sulfonyl]amino]carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt



The compound of Example 111 (500 mg, 0.095 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (350 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 113

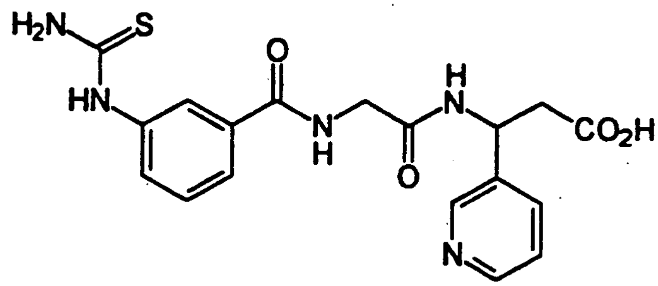
Preparation of ethyl β-[[2-[[[3-[(aminothi xomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoate, trifluoroacetate salt



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-(3-pyridyl)propionate (2 g, 0.64 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzoyl isothiocyanate (600 mg, 0.75 mmol). After complete reaction the solvent was removed under reduced pressure. To the resulting oil was added methanol (50 mL) followed by K_2CO_3 (2 g) and the reaction was left to stir until the hydrolysis was complete. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (980 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 114

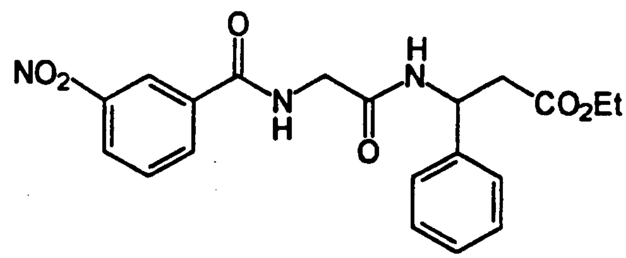
Preparation of β-[[2-[[[3-[(amin thiox m thyl)amino]-phenyl]carbonyl]amino]acetyl]amino]pyridin -3-propanoic acid, trifluoroacetate salt



The compound of Example 113 (500 mg, 0.095 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (350 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 115

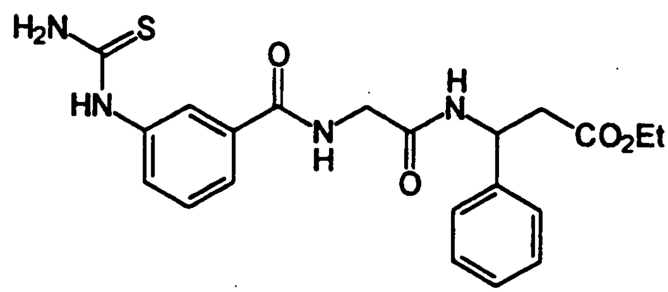
Pr paration of DL-ethyl(3-nitrobenzoylglycyl)-3-amido-phenyl propionate



N,N'-disuccinimidyl carbonate (14 g, 5.5 mmol) was added to 3-nitro-benzoyl glycine (10 g, 4.5 mmol) in dry dimethylformamide (30 mL) followed by dimethylaminopyridine (200 mg). After a period of 1 hour DL-ethyl-3-amino-3-phenylpropionate hydrochloride (12 g, 4.6 mmol) in 20% aqueous potassium carbonate (50 mL) was added in one portion. After complete reaction the product was collected by filtration (12 g, 87% yield). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 116

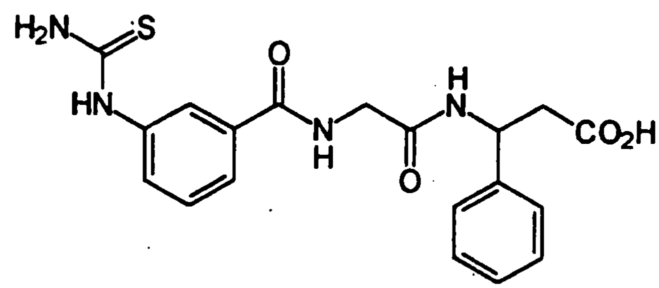
Preparation of ethyl β-[[2-[[[3-[(aminothioxomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoate



The compound of Example 115 (2 g, 0.64 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzoyl isothiocyanate (600 mg, 0.75 mmol). After complete reaction the solvent was removed under reduced pressure. To this oil, methanol (50 mL) was added followed by K_2CO_3 (2 g) and the reaction was left to stir until the hydrolysis was complete. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (980 mg). MS and NMR were consistent with the proposed structure.

Example 117

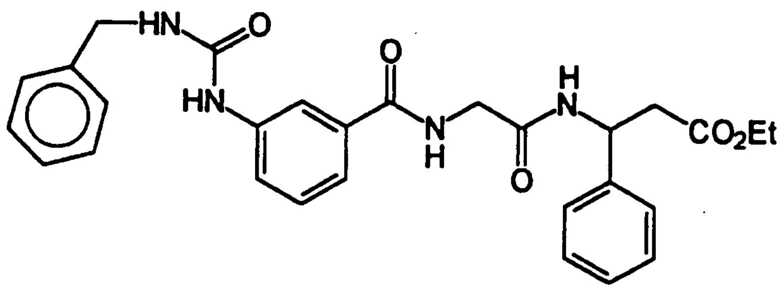
Preparation of β-[[2-[[[3-[(aminothioxomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]benzenepropanoic acid



The product of Example 116 (500 mg, 0.095 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (350 mg). MS and ^1H-NMR were consistent with the proposed structure.

Example 118

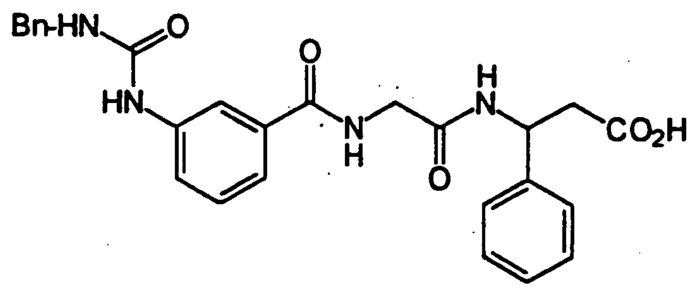
Preparation of ethyl β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]benzenepropanoate



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-phenyl propionate (2 g, 0.62 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzyl isocyanate (700 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product filtered. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.5 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 119

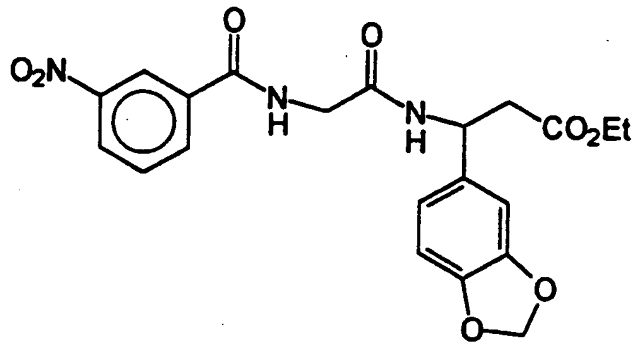
Preparation of β-[[2-[[[3-[[[(phenylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid



The product of Example 118 (400 mg, 0.094 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (200 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 120

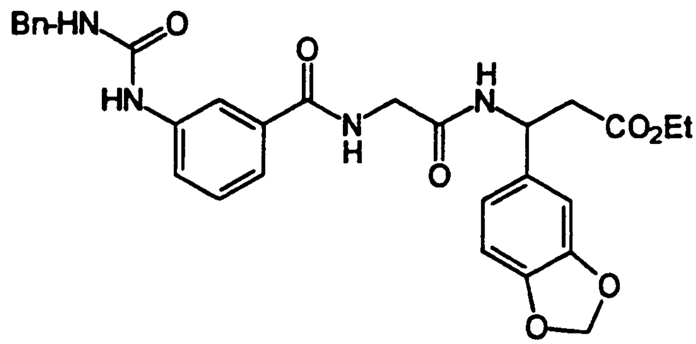
Preparation f β-[[2-[[(3-nitrophenyl)carbonyl]amino]-acetyl]amino]-1,3-benzodioxole-5-propanoate



N,N'-disuccinimidyl carbonate (14 g, 5.5 mmol) was added to 3-nitro-benzoyl glycine (10 g, 4.5 mmol) in dry dimethylformamide (30 mL) followed by dimethylaminopyridine (200 mg). After a period of 1 hour ethyl DL-3-amino-3-piperinalpropionate hydrochloride (7 g, 4.6 mmol) in 20% aqueous potassium carbonate (50 mL) was added in one portion. After complete reaction the product was collected by filtration (14 g, 97% yield). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 121

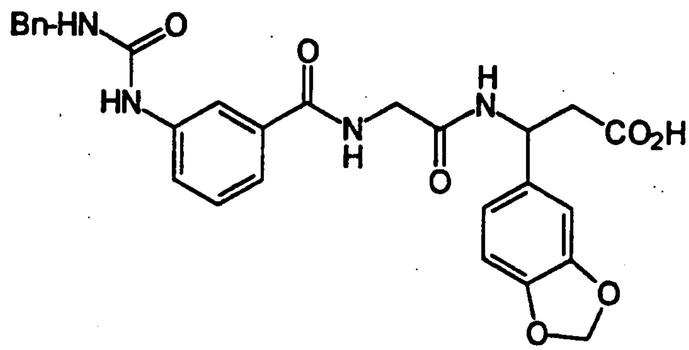
Preparation of ethyl β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-1,3-benzodioxole-5-propanoate



The compound of Example 120 (2 g, 0.62 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by benzyl isocyanate (700 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product filtered. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.5 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 122

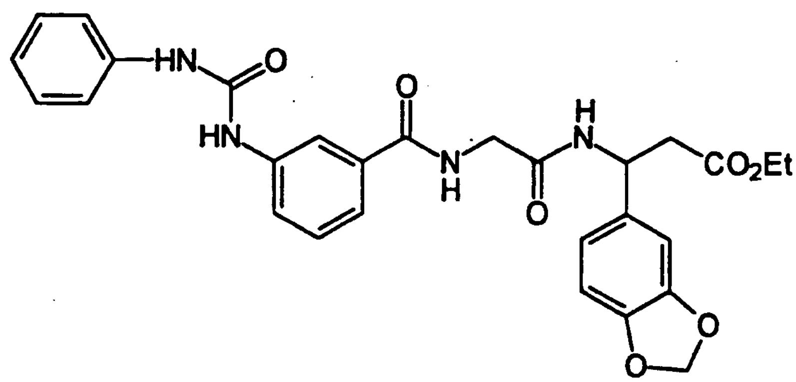
Preparation f β-[[2-[[[3-[[[(phenylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-1,3-benzodioxole-5-propanoic acid



The compound of Example 121 (400 mg, 0.094 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (200 mg). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 123

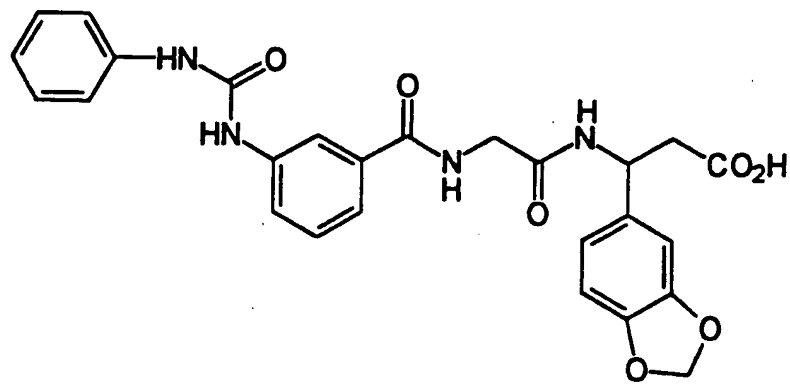
Preparation of ethyl β-[[2-[[[3-3-[[(phenylamino)carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]-1,3-benzodioxole-5-propanoate



DL-ethyl(3-nitrobenzoylglycyl)-3-amido-3-piperidinal propionate (2 g, 0.62 mmol) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Acetonitrile (5 mL) was added to the crude aniline followed by phenyl isocyanate (700 mg, 0.75 mmol). The solution turned to a solid. Diethyl ether was added and the product filtered. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.5 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Example 124

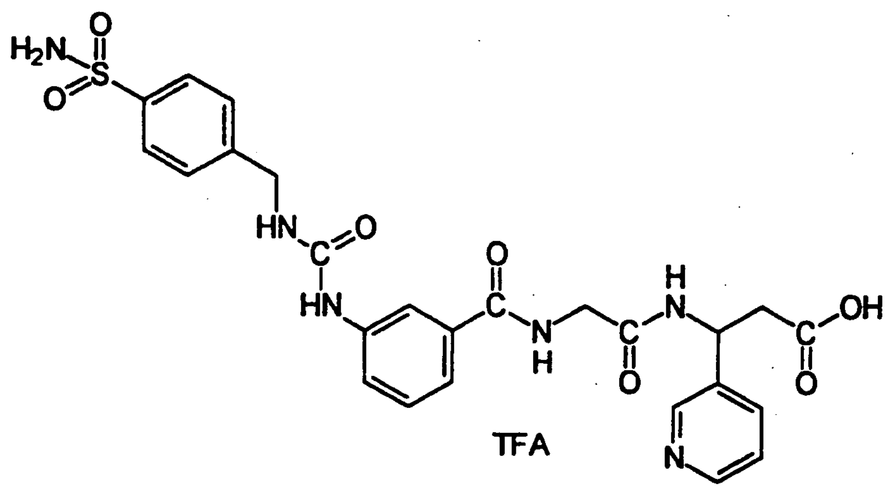
Preparation of β-[[2-[[[3-3-[[(phenylamino)-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-1,3-benzodioxole-5-propanoic acid



The product of Example 123 (400 mg, 0.094 mmol) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg, 0.4 mmol). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (200 mg). MS and NMR were consistent with the proposed structure.

Example 126

Preparati n of β-[[2-[[[3-[[[[(4-(aminosulfonyl)-phenylmethyl]amino]carbonyl]amino]phenyl]carbonyl]-amino]acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt



Step A

To 4-(aminomethyl)-benzenesulfonamide hydrochloride hydrate (Aldrich) (6 g) in acetonitrile was added 3-ethoxycarbonyl phenylisocyanate (Lancaster) (5 g) and triethylamine (5 ml). The reaction was stirred for 1 hour. The solvent was removed under reduced pressure to give a solid mass. Water was added and the solid filtered (10.2 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step B

The compound from Step A (10 g) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (4 g). The reaction mixtur was stirred at 25°C, and monitor d by HPLC. After complete hydrolysis (4-6 hours) 10% aqueous HCl was added until pH = 2. The product was purified by filtration to give

a white solid (7 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step C

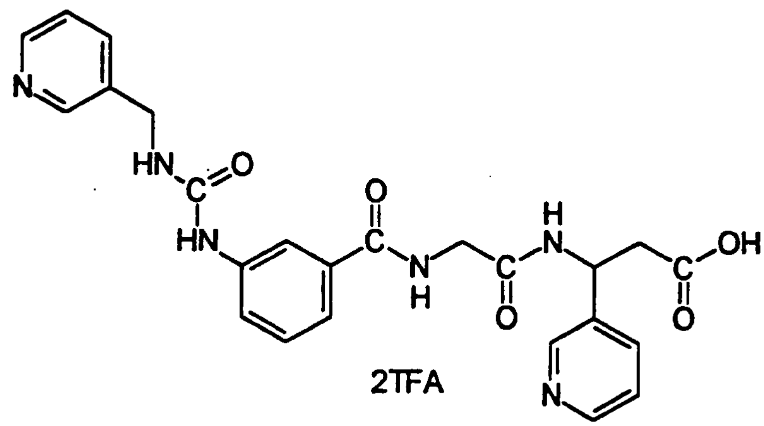
N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added to the carboxylic acid-urea of 4-(aminomethyl)benzenesulfonamide and 3-ethoxycarbonyl phenylisocyanate (1 g, 0.5 mmol) [See Scheme V(**A13**)] in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour the compound from Example 1, Step C was added (2.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) in one portion. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.2 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step D

The compound from Step C (600 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 500 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 127

Preparati n of β-[[2-[[[3-[[[(3-pyridinylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid, bis trifluoroacetate salt



2TFA

Step A

To 3-pyridinemethylamine (Aldrich) (6 g) in acetonitrile was added 3-ethoxycarbonyl phenylisocyanate (Lancaster) (5 g) and triethylamine (5 ml). The reaction was stirred for 1 hour. The solvent was removed under reduced pressure to give a solid mass. Water was added and the solid filtered (12 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step B

The compound from Step A (10 g) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (4 g). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (4-6 hours) 10% aqueous HCl was added until pH = 2. The product was purified by filtration to give a white solid (5.6 g). MS and ^{1}H-NMR were consistent with the propos d structur .

Step C

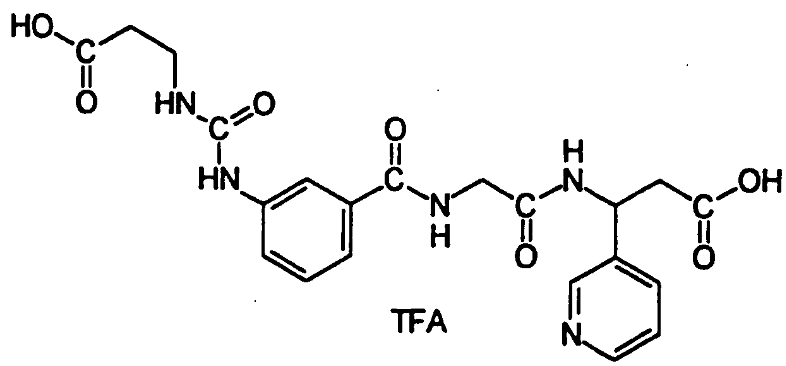
N,N′-Disuccinimidyl carbonat (DSC) (1.4 g, 0.5 mmol) was added to the carboxylic acid-ur a of 3-pyridine methylamine (Aldrich) and 3-ethoxycarbonyl phenylisocyanate (1 g, 0.5 mmol) [See Scheme V(A13)] in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour the compound from Example 1, Step C was added (2.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) in one portion. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.1 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step D

The compound from Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 430 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 129

Preparation f β-[[2-[[[3-[[[(2-carboxyethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, trifluoroacetate salt



Step A

The compound of Example 104 (1.5 g) was dissolved in ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (500 mg) was added and the mixture was hydrogenated under 50 psi in a Parr apparatus for a period of 1.5 hours. The palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*.

Step B

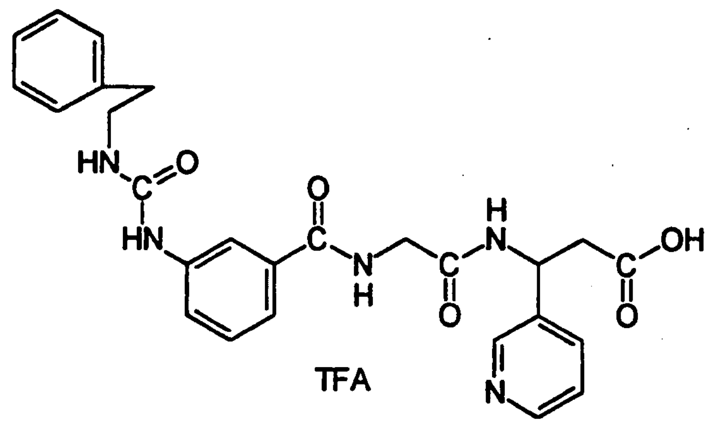
Acetonitrile (5 mL) was added to the crude aniline from Step A followed by ethyl isocyanatopropionate (Aldrich) (800 mg) and stirred for 1 hour. The solvent was removed under reduced pressure to give a solid. Diethyl ether was added and the solid was filtered to give a tan colored solid. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 500 mg of a white solid. MS and ^{1}H-NMR wer consistent with the proposed structur .

Step C

The compound from Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 220 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 130

Preparation of β-[[2-[[[3-[[[(2-phenylethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, trifluoroacetate salt



TFA

Step A

To phenylethylamine hydrochloride (Aldrich) (6 g) in acetonitrile was added 3-ethoxycarbonyl phenylisocyanate (Lancaster) (5 g) and triethylamine (5 ml). The reaction was stirred for 1 hour. The solvent was removed under reduced pressure to give a solid mass. Water was added and the solid filtered (11 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step B

The compound from Step A (10 g) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (4 g). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (4-6 hours) 10% aqueous HCl was added until pH = 2. The product was purified by filtration to give a white solid (5.6 g). MS and ^{1}H-NMR were consistent with th proposed structure.

Step C

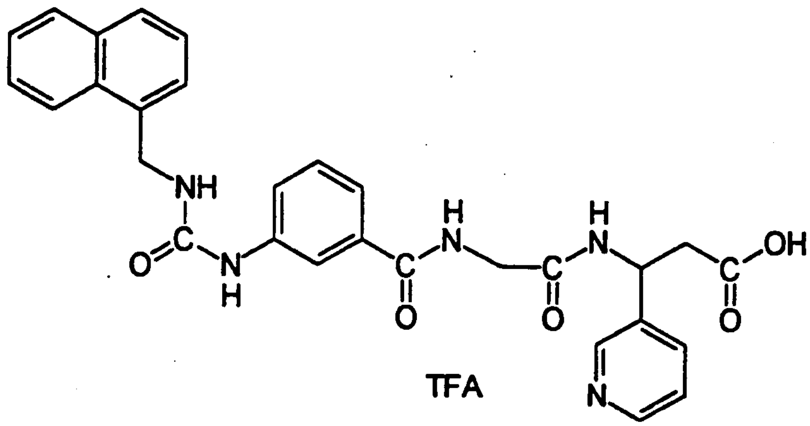
N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added t the carb xylic acid-urea of phenylethylamine and 3-ethoxycarbonyl phenylisocyanate (1 g, 0.5 mmol) [See Scheme V(A13)] in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour the compound from Example 1, Step C was added (2.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) in one portion. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.0 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step D

The compound from Step C (800 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 633 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 131

Preparation of β-[[2-[[[3-[[[(1-naphthal nylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]acetyl]-amino]pyridine-3-propanoic acid, trifluoroacetate salt



Step A

To 1-naphthalene methylamine (Aldrich) (5 g) in acetonitrile was added 3-ethoxycarbonyl phenylisocyanate (Lancaster) (5 g) and triethylamine (5 ml). The reaction was stirred for 1 hour. The solvent was removed under reduced pressure to give a solid mass. Water was added and the solid filtered (9 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step B

The compound from Step A (8 g) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (3 g). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (4-6 hours) 10% aqueous HCl was added until pH = 2. The product was purified by filtration to give a white solid (5.6 g). MS and ^{1}H-NMR were consist nt with the proposed structure.

Step C

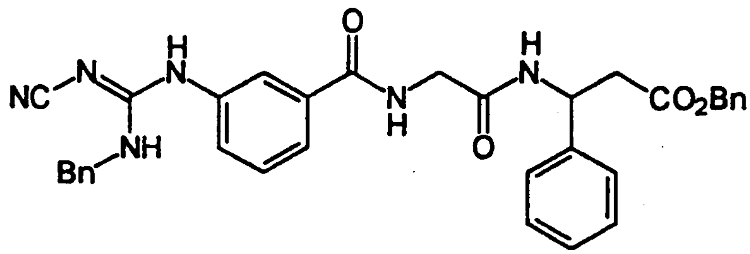
N,N'-Disuccinimidyl carbonate (DSC) (1.4 g, 0.5 mmol) was added to th carboxylic acid-urea of 1-naphthalene methylamine and 3-ethoxycarbonyl phenylisocyanate (1 g, 0.5 mmol) [See Scheme V(A13)] in dry dimethylformamide (20 mL) followed by dimethylaminopyridine (100 mg). After a period of 1 hour the compound from Example 1, Step C was added (2.2 g, 0.5 mmol) in DMF/NMM (1:1) (5.0 mL) in one portion. After complete reaction the product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in a white solid (1.0 g). MS and ^{1}H-NMR were consistent with the proposed structure.

Step D

The compound from Step C (600 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction mixture was stirred at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH=2. The product was purified by reverse phase chromatography (water/acetonitrile) and lyophilized to result in 410 mg of a white solid. MS and ^{1}H-NMR were consistent with the proposed structure.

Example 132

Preparation of phenylm thyl β-[[2-[[[3-[[(cyanoimino)-phenylm thylamino)methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoate

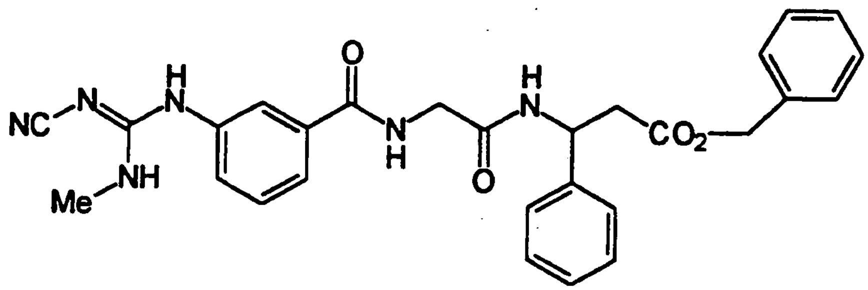


To a stirred solution of the product of Example I (140 mg, 0.52 mM), in methylene chloride (25 ml) at 0°, triethylamine, (0.5 ml), DMAP (10 mg), EDCl (95 mg) and the compound from Example V (215 mg, 0.52 mM) were added. The reaction mixture was stirred at 0°C for 15 minutes, allowed to attain room temperature and then stirred for another 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated aqueous $NaHCO_3$ and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product. The crude product was further purified by chromatography on silica (eluant:ethyl acetate) and excess solvent removed to afford the title compound (88 mg) as a clear oil.

NMR and MS were consistent with the proposed structure.

Example 133

Preparation of phenylm thyl β-[[2-[[[3-[[(cyan imino)-methylamino)methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoate

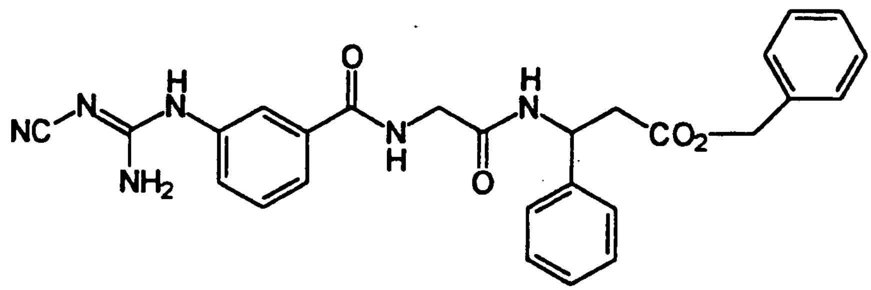


To a stirred solution of the product of Example J (90 mg, 0.41 mM), in methylene chloride (25 ml) at 0°, triethylamine, (0.5 ml), DMAP (10 mg), EDCl (95 mg) and the compound from Example V (215 mg, 0.52 mM) were added. The reaction mixture was stirred at 0°C for 15 minutes, allowed to attain room temperature and then stirred for another 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated $NaHCO_3$ and finally water again. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product. The crude product was further purified by chromatography on silica (eluant:ethyl acetate) and excess solvent removed to afford the title compound (80 mg) as a clear oil.

NMR was consistent with the proposed structure.

Example 134

Preparation of phenylmethyl β-[[2-[[[3-[[(cyanoimino)-(amino)methyl]amino]phenyl]carbonyl]amino]acetyl]-amino]benzenepropanoate

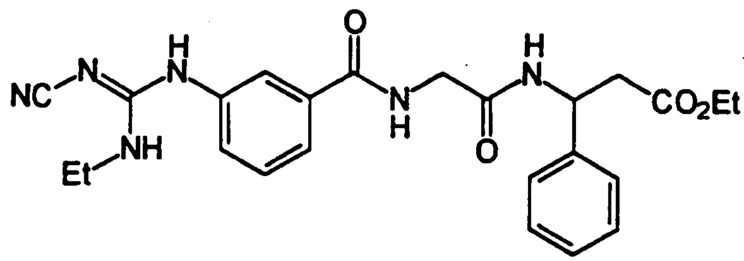


To a stirred solution of the product of Example K (212 mg, 1.0 mM), in methylene chloride (25 ml) at 0°, triethylamine, (0.5 ml), DMAP (10 mg), EDCl (95 mg) and the compound from Example V (215 mg, 0.52 mM) were added. The reaction mixture was stirred at 0°C for 15 minutes, allowed to attain room temperature and then stirred for another 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated $NaHCO_3$ and again with water. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product. The crude product was further purified by chromatography on silica (eluant:ethyl acetate) and excess solvent removed to afford the title compound (285 mg) as a clear oil.

NMR was consistent with the proposed structure.

Example 135

Preparation of ethyl β-[[2-[[[3-[[(cyanoimino)-(ethylamino)methyl]amino]phenyl]carbonyl]amino]acetyl]-amino]benzenepropanoate



To a stirred solution of the product of Example L (464 mg, 2.0 mM), DL ethyl β-[(2-amino-1-oxoethyl)amino]phenyl-3-propanoate (728 mg, 2.0 mM) [prepared according to Example 1 (Step B, C and D) replacing DL-3-amino-3-(3-pyridyl)propionic acid with an equivalent amount of DL-3-amino-3-(3-phenyl)propionic acid], triethylamine (2.0 ml)and DMAP (20 mg) in methylene chloride (15 ml) at 0°C, EDCl (191 mg) was added. The reaction mixture was stirred at 0°C for 15 minutes, allowed to attain room temperature and then stirred for another 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated $NaHCO_3$ and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product. The crude product was further purified by reverse phase HPLC on a C18 column (eluant:0.5% TFA-water/ acetonitrile) to afford the title compound (280 mg) as a white solid.

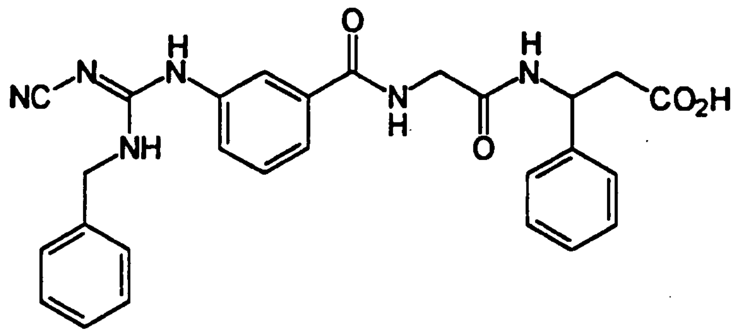
Analysis for $C_{24}H_{28}N_6O_4$ 0.3 H_2O:

Calcd:	C, 61.34;	H, 6.13;	N, 17.88.	
Found:	C, 61.17;	H, 6.26;	N, 17.85.	

NMR was consistent with the proposed structure.

Example 136

Preparation of β-[[2-[[[3-[[(cyanoimino)-[(phenylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoic acid



To a stirred solution of the compound from Example 132 (88 mg) in methanol (2 ml) and THF (2 ml), 1N sodium hydroxide (2 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, evaporated and the residue dissolved in water. The resulting solution was adjusted to pH 4 with 1N hydrochloric acid and the resulting solid was isolated by filtration. The filtrate was further washed with water followed by diethyl ether.

This afforded the title compound (62 mg) as a white solid.

Analysis for $C_{27}H_{26}N_6O_4$ 0.5 H_2O 0.25 Et_2O:

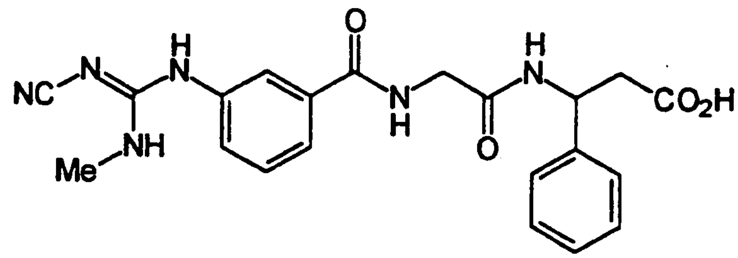
Calcd: C, 63.93; H, 5.65; N, 15.97.

Found: C, 63.96; H, 5.73; N, 15.81.

NMR was consistent with the proposed structure.

Example 137

Preparation of β-[[2-[[[3-[[(cyanoimino)(m thylamino)-methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid



To a stirred solution of the compound from Example 133 (240 mg) in methanol (3 ml) and THF (3 ml), 1N sodium hydroxide (3 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, evaporated and the residue dissolved in water. The resulting solution was adjusted to pH 4 with 1N hydrochloric acid and extracted with ethyl acetate/MeOH. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated to afford a clear gum. The crude product was further purified by reverse phase HPLC on a C18 column (eluant:0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound (88 mg) as a white solid.

Analysis for $C_{21}H_{22}N_6O_4$ 0.55 TFA:

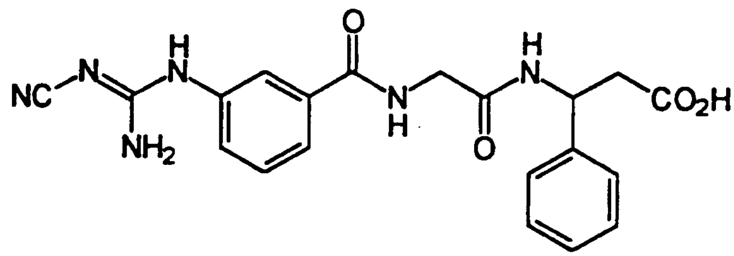
Calcd: C, 54.71; H, 4.68; N, 17.32.

Found: C, 54.92; H, 4.70; N, 16.93.

NMR was consistent with the proposed structure.

Example 138

Preparation of β-[[2-[[[3-[[amino(cyanoimino)methyl]-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid



To a stirred solution of the compound from Example 134 (285 mg) in methanol (3 ml) and THF (3 ml), 1N sodium hydroxide (3 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, evaporated and the residue dissolved in water. The resulting solution was adjusted to pH 4 with 1N hydrochloric acid and extracted with ethyl acetate/MeOH. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated to afford an off white solid. The crude product was further purified by reverse phase HPLC on a C18 column (eluant:0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound (65 mg) as a white solid.

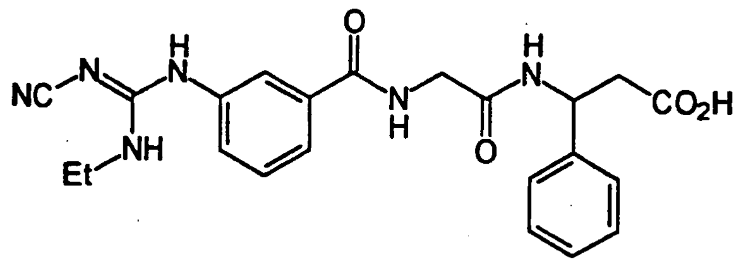
Analysis for $C_{20}H_{20}N_6O_4$ 1.25 H_2O, 0.3 MeOH:

Calcd:	C, 55.35; H, 5.42; N, 19.08.
Found:	C, 55.70; H, 5.01; N, 18.69.

NMR was consistent with the proposed structure.

Example 139

Preparation of β-[[2-[[[3-[[(cyanoimino)(thylamino)-methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid



To a stirred solution of the compound from Example 135 (285 mg) in methanol (3 ml) and THF (3 ml) was added, 1N sodium hydroxide (3 ml). The reaction mixture was stirred at room temperature for 2 hours, evaporated and the residue dissolved in water. The resulting solution was adjusted to pH 4 with 1N hydrochloric acid and extracted with ethyl acetate/MeOH. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated to afford an off white solid. The crude product was further purified by RPHPLC on a C18 column (eluant:0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound (180 mg) as a white solid.

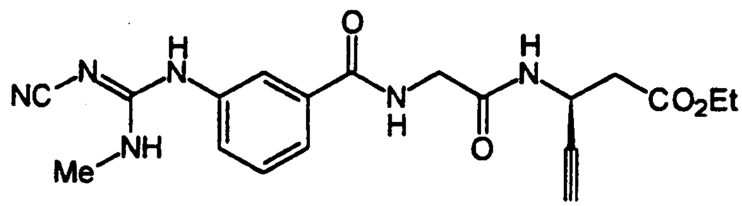
Analysis for $C_{22}H_{24}N_6O_4$ 0.35 H_20:

Calcd:	C, 59.68; H, 5.62; N, 18.98.
Found:	C, 59.80; H, 5.61; N, 18.59.

NMR was consistent with the proposed structure.

Example 140

Preparation of ethyl 3S-[[2-[[[3-[[(cyanoimino)-(methylamino)methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoate



To a stirred solution of the product of Example J (436 mg, 2.0 mM), ethyl DL β-[(2-amino-1-oxoethyl)amino]-4-pentynoate (624 mg, 2.0 mM) [prepared according to Example 1 (Step B, C and D) replacing DL-3-amino-3-(3-pyridyl)propionic acid with an equivalent amount of ethyl-3S-amino-4-pentynoate (J. Med. Chem., 1995, <u>38</u>, 3378)], triethylamine (2.0 ml) and DMAP (20 mg) in methylene chloride (20 ml) at 0°C, EDCl (382 mg, 2.0 mM) was added. The reaction mixture was stirred at 0°C for 15 minutes, allowed to attain room temperature and then stirred for another 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum which was dissolved in ethyl acetate. The resulting solution was washed with water, saturated $NaHCO_3$ and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford the crude product. The crude product was further purified by RPHPLC on a C18 column (eluant:0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound (280 mg) as a white solid.

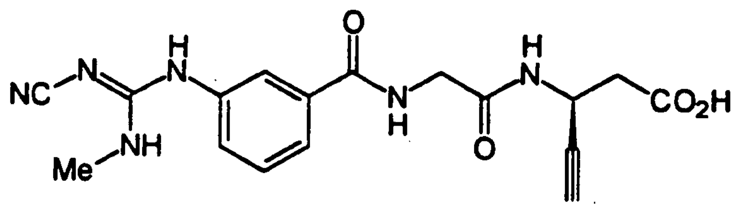
NMR was consistent with the proposed structure.

Analysis for $C_{17}H_{18}N_6O_4$ 0.45 TFA:

Calcd:	C, 50.99; H, 4.41; N, 19.93.
Found:	C, 51.28; H, 4.70; N, 19.72.

Example 141

Preparation of 3S-[[2-[[[3-[[(cyanoimino)(methylamino)-methyl]amino]phenyl]carbonyl]amino]acetyl]amino]-4-pentynoic acid



To a stirred solution of the compound from Example 140 (280 mg) in methanol (3 ml) and THF (3 ml), 1N sodium hydroxide (3 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, evaporated and the residue dissolved in water. The resulting solution was adjusted to pH 4 with 1N hydrochloric acid and extracted with ethyl acetate/MeOH. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated to afford an off white solid. The crude product was further purified by reverse phase HPLC on a C18 column (eluant:0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound (122 mg) as a white solid.

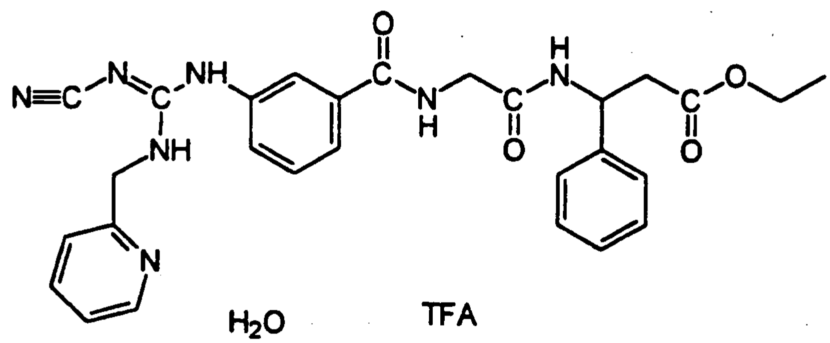
Analysis for $C_{17}H_{18}N_6O_4$ 0.45 TFA:

Calcd:	C, 50.99; H, 4.41; N, 19.93.
Found:	C, 51.28; H, 4.70; N, 19.72.

NMR was consistent with the proposed structure.

Example 143

Preparation of ethyl β-[[2-[[[3-[[(cyanoimino)[2-pyridinylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoate, trifluoroacetate salt



The title compound was synthesized following the procedure described in Example 135 except the compound of Example L was replaced with an equivalent amount of Example O. This afforded the title compound.

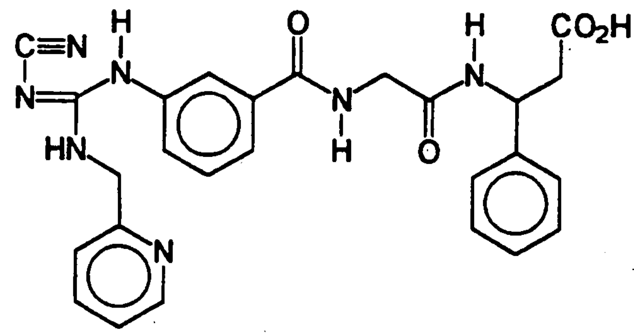
NMR was consistent with the proposed structure.

$C_{28}H_{29}N_7O_4$ 1TFA, $1H_2O$:

Calcd.:	C, 54.63; H, 4.89; N, 14.86
Found:	C, 54.28; H, 4.58; N, 14.63

Example 144

Preparation of β-[[2-[[[3-[[(cyan imino)[2-pyridinylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoic acid, bis(trifluoroacetate) salt



The title compound was prepared following the procedure described in Example 136 except the compound of Example 132 was replaced with an equivalent amount of the compound of Example 143. This afforded the title compound as a white solid.

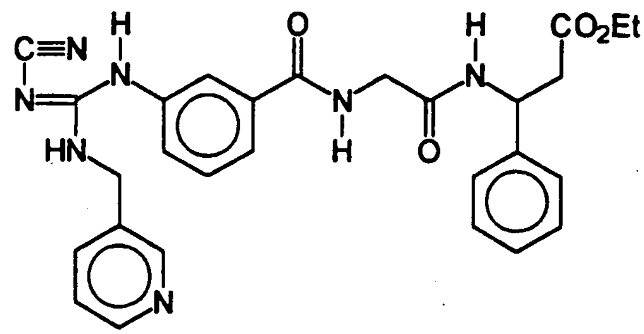
NMR was consistent with the proposed structure.

$C_{26}H_{25}N_7O_4$ 2TFA, $1H_2O$:

Calcd.:	C, 48.33; H, 3.92; N, 13.15
Found:	C, 48.21; H, 3.59; N, 13.19

Example 145

Preparation of ethyl β-[[2-[[[3-[[(cyanoimino)[3-pyridinylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoate, trifluoroacetate salt



The title compound was prepared following the procedure described in Example 135 except the compound of Example L was replaced with an equivalent amount of the compound of Example Q. This afforded the title compound as a white solid.

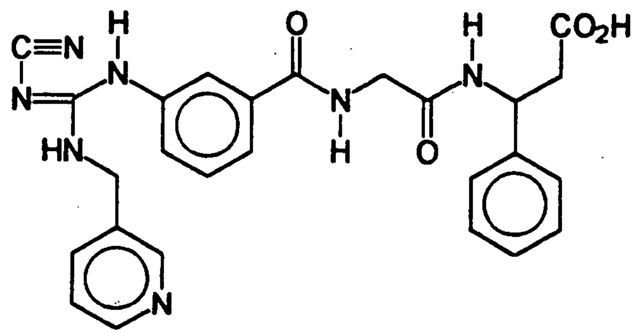
NMR was consistent with the proposed structure.

$C_{28}H_{29}N_7O_4$ 1TFA, $1H_2O$:

Calcd.:	C, 54.63; H, 4.89; N, 14.86
Found:	C, 54.24; H, 4.85; N, 14.41

Example 146

Preparation f β-[[2-[[[3-[[(cyanoimino)[3-pyridinylmethyl)amino]methyl]amino]phenyl]carbonyl]-amino]acetyl]amino]benzenepropanoic acid, bis(trifluoroacetate) salt



The title compound was prepared following the procedure described in Example 136 except the compound of Example 132 was replaced with an equivalent amount of the compound of Example 145, to yield the title compound as a white solid.

NMR was consistent with the proposed structure.

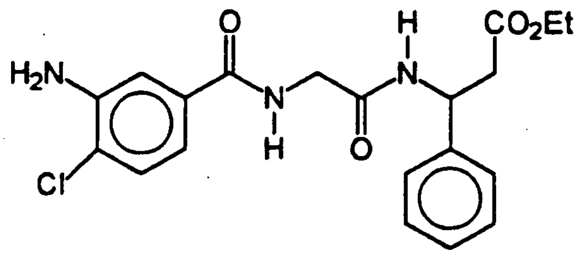
$C_{26}H_{25}N_7O_4$ 2TFA, $0.25H_2O$:

Calcd.: C, 49.22; H, 3.79; N, 13.39

Found: C, 49.50; H, 4.05; N, 13.64

Example 147

Preparation of ethyl β-[[2-[[(3-amino-4-chlorophenyl)carbonyl]amino]acetyl]amino]-benzenepropanoate

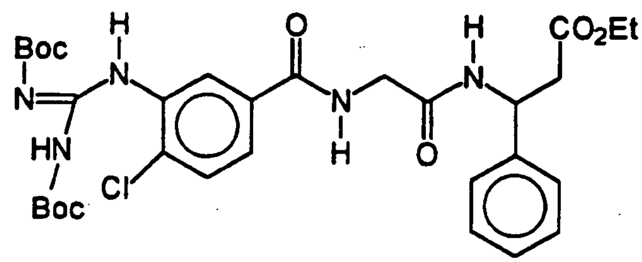


The title compound was prepared following the procedure described in Example 135 except the compound of Example L was replaced with an equivalent amount of 3-amino-4-chlorobenzoic acid to yield the title compound as brown solid (93.5% yield).

The NMR was consistent with the proposed structure.

Example 148

Preparation of thyl β-[[2-[[[4-chloro-3-[[[[(1,1-dimethylethoxy)carbonyl]amino][[(1,1-dimethylethoxy)-carbonyl]imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoate



To a stirred solution of the product of Example 147 (400 mg, 1.13 mM), N,N[1]-bis-Boc-thiourea (311 mg, 1.13 mM) [Edwin J. Iwanowicz et al., Synthetic Communications, 23(10)(1993) 1443-1445], DMF (6 ml), triethylamine (0.6 ml) was added $HgCl_2$ (360 mg) at 0-5°C. The mixture was stirred at 0-5°C for 15 minutes and was allowed to warm to room temperature. The mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (50 ml) and was filtered through celite under vacuum. The filtrate was concentrated *in vacuo* to afford an oily gum which was purified through flash silica column using 100% ethyl acetate as an eluent to afford the title compound (254 mg) as a white solid.

NMR was consistent with the proposed structure.

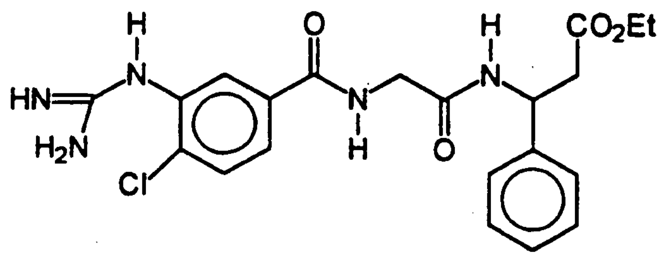
$C_{31}H_{40}N_5O_8$ 1.5 H_2O:

Calcd.: C, 55.31; H, 6.44; N, 10.40

Found: C, 55.17; H, 6.50; N, 10.56

Example 149

Preparation of ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]-4-chlorophenyl)carbonyl]amino]acetyl]amino]-benzenepropanoate, trifluoroacetate salt



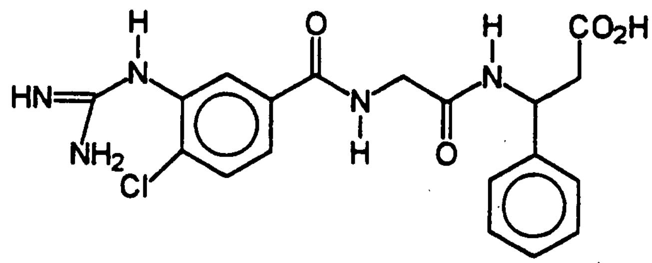
To a stirred solution of Example 148 (420 mg) in methylene chloride (5 ml) was added TFA (9 ml) at 0°C. The mixture was warmed to room temperature and stirred at room temperature for 1½ hours. The mixture was concentrated *in vacuo* to afford the crude product. The crude product was further purified by reverse phase HPLC on a C18 column (eluant: 0.5% TFA-H_2O/acetonitrile) and lyophilized to afford the title compound (68 mg) as a white solid.

$C_{21}H_{24}N_5O_4Cl$ 1.0 TFA 0.45 H_2O:

Calcd.:	C, 48.63; H, 4.60; N, 12.33
Found:	C, 48.28; H, 4.16; N, 12.13

Example 150

Preparation f β-[[2-[[[3-[(aminoiminomethyl)amino]-4-chlorophenyl)carbonyl]amino]acetyl]amino]-benzenepropanoic acid



The title compound was prepared following the procedure described in Example 136 except the compound of Example 132 was replaced with an equivalent amount of the compound of Example 149 to yield the title compound as a white solid.

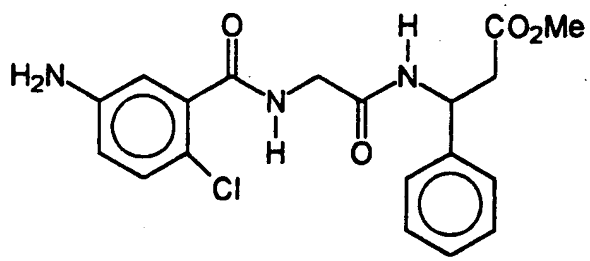
The NMR was consistent with the proposed structure.

$C_{19}H_{20}N_5O_4Cl$ 1.5 TFA:

Calcd.:	C, 44.87; H, 3.68; N, 11.89
Found:	C, 44.54; H, 3.80; N, 11.43

Example 152

Preparation of methyl β-[[2-[[(5-amino-2-chlorophenyl)carbonyl]amino]acetyl]amino]-benzenepropanoate

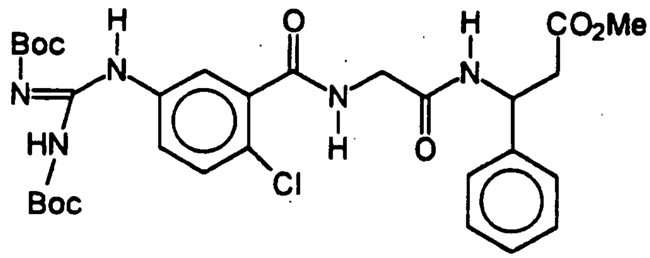


The title compound was prepared following the procedure described in Example 135 except the compound of Example L was replaced with an equivalent amount of 3-amino-6-chlorobenzoic acid to yield the title compound as pale brown solid.

The NMR was consistent with the proposed structure.

Example 153

Preparation of methyl β-[[2-[[[2-chlor -5-[[[[(1,1-dim thylethoxy)carbonyl]amino][[1,1-dimethylethoxy)-carbonyl]imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoate

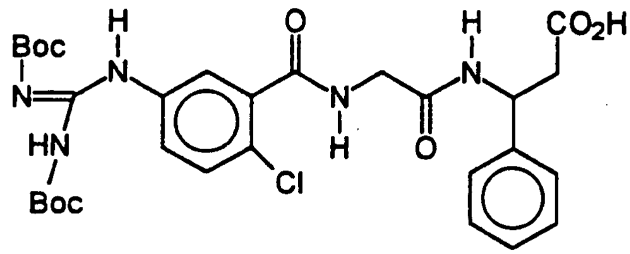


The title compound was prepared following the procedure described in Example 148 except the compound of Example 146 was replaced with an equivalent amount of the compound of Example 152 to yield the title compound as a white solid.

The NMR was consistent with the proposed structure.

Example 154

Preparation f β-[[2-[[[2-chloro-5-[[[[(1,1-dimethylethoxy)carbonyl]amino][[(1,1-dimethyl thoxy)-carbonyl]imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoic acid

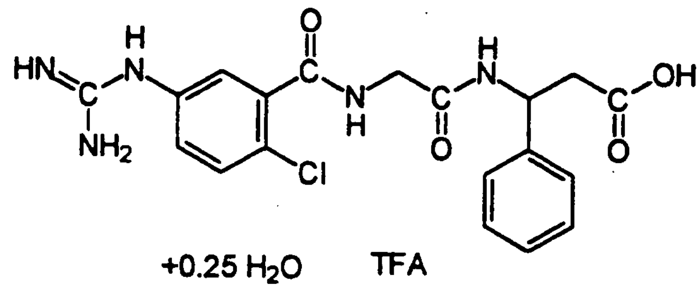


The title compound was prepared following the procedure described in Example 136 except the compound of Example 132 was replaced with an equivalent amount of the compound of Example 153 to yield the title compound as a white solid.

The NMR was consistent with the proposed structure.

Example 155

Preparation of β-[[2-[[[5-[(aminoiminomethyl)amino]-2-chlorophenyl]carbonyl]amino]acetyl]amino]benzene-propanoic acid, trifluoroacete salt



The title compound was prepared following the procedure described in Example 150 except the compound of Example 149 was replaced with an equivalent amount of the compound of Example 154 to yield the title compound as a white solid.

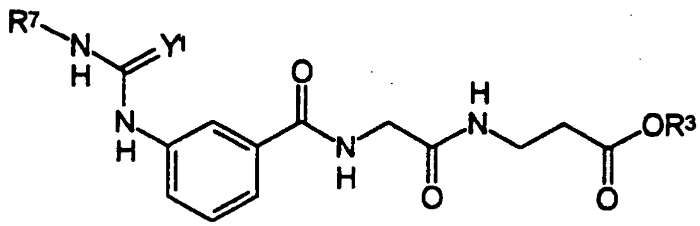
NMR was consistent with the proposed structure.

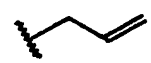
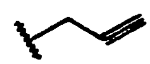
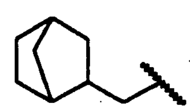
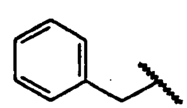
$C_{19}H_{20}N_5O_4Cl$ 1TFA, 0.25 H_2O:

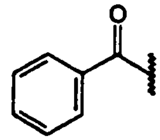
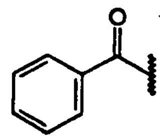
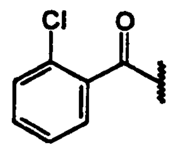
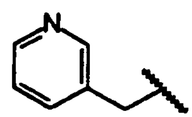
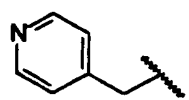
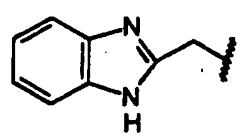
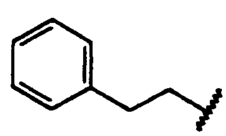
Calcd.:	C, 47.02; H, 4.04; N, 13.06
Found:	C, 47.17; H, 3.85; N, 12.72

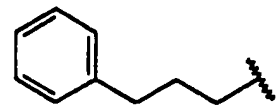
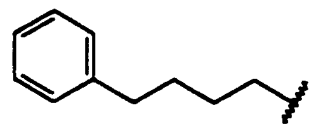
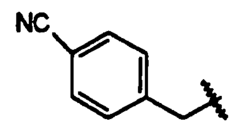
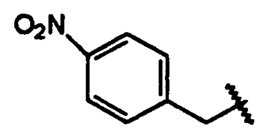
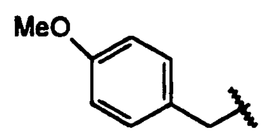
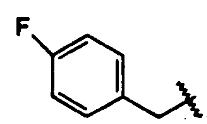
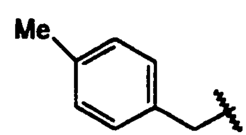
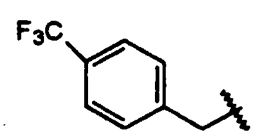
Example 156

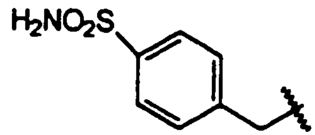
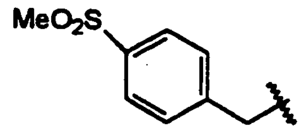
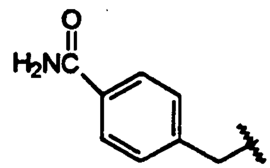
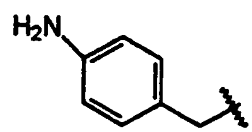
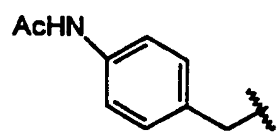
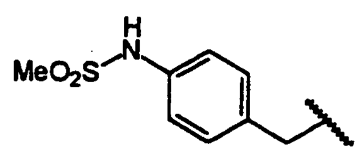
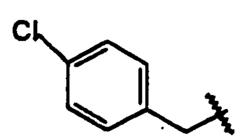
Using the procedures of the present disclosure and starting with the requisite reagents, the following compounds are prepared:

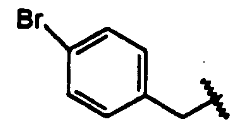
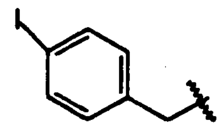
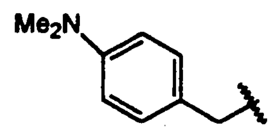
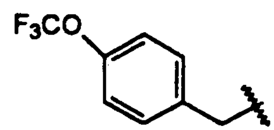
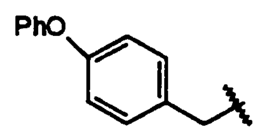
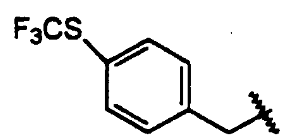
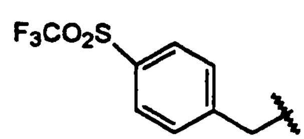


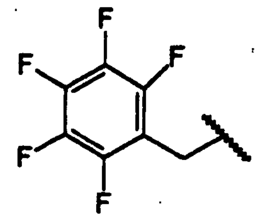
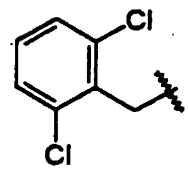
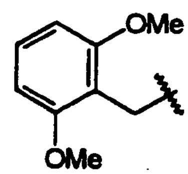
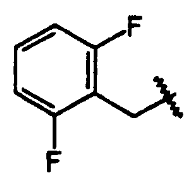
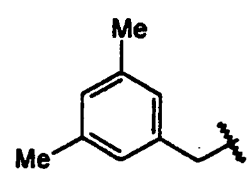
R^3	Y^1	R^7
Et or H	O	n-Bu
Et or H	O	i-Pr
Et or H	O	t-Bu
Et or H	O	n-Pr
Et or H	O	
Et or H	O	
Et or H	O	cyclohexyl
Et or H	O	cyclohexylmethyl
Et or H	O	
Et or H	S	
Et or H	S	cyclohexylmethyl
Et r H	S	3-pyridyl

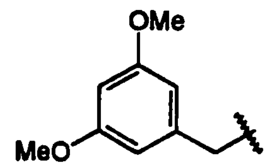
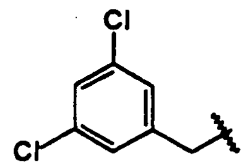
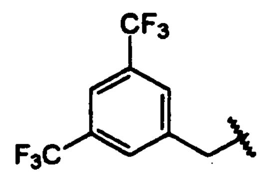
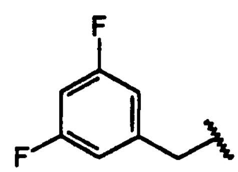
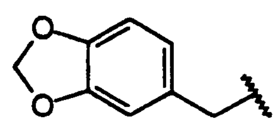
R^3	Y^1	R^7
Et or H	O	
Et or H	S	
Et or H	S	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

R^3	Y^1	R^7
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

R^3	Y^1	R^7
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

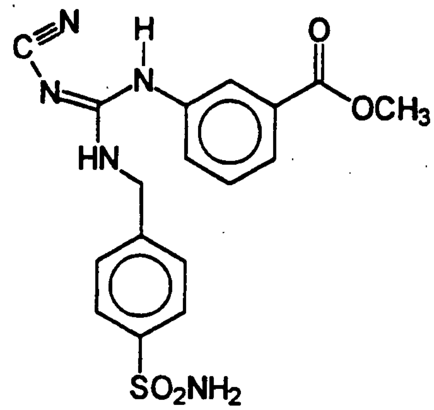
R^3	Y^1	R^7
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

R^3	Y^1	R^7
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

R^3	Y^1	R^7
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	
Et or H	O	

EXAMPLE AA

Preparation of

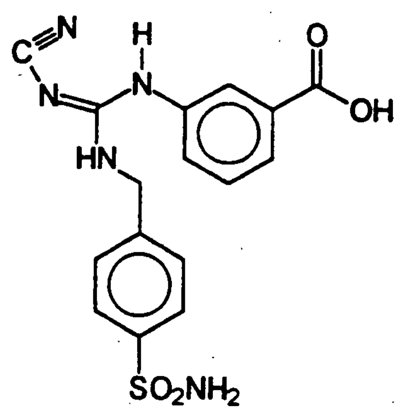


The above compound was prepared following the procedure described in Example E, replacing benzylamine with p-aminomethyl benzenesulfonamide. The above compound was obtained as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE AB

Preparation of

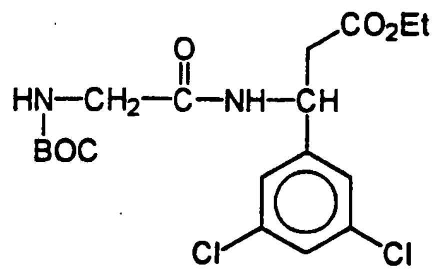


The above compound was prepared following the procedure described in Example I, replacing the compound of Example E with the compound of Example R. The above compound was obtained as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE AC

Preparation of

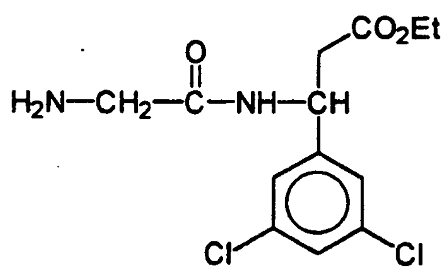


The above compound was prepared following the procedure described in Example 140, replacing the compound of Example J with N-t-Boc glycine and replacing DL ethyl β-[(2-amino-1-oxoethyl)amino]-4-pentynoate with ethyl-DL-3-amino-3-(3,5-dichlorophenyl)propionate. The above compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE AD

Preparation of

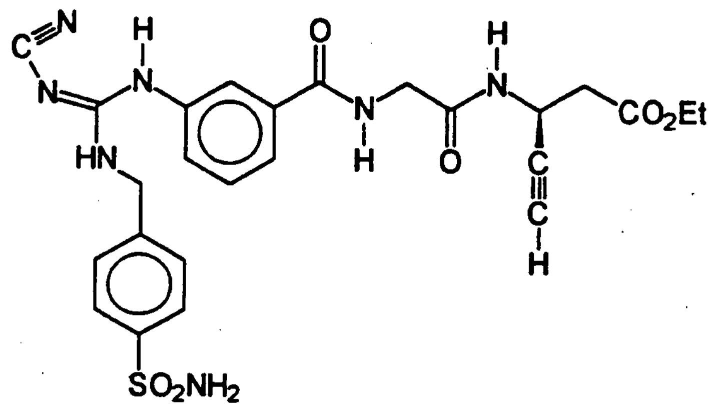


The above compound was prepared following the procedure described in Example 161, replacing the compound of Example 159 with that of Example AC. The above compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 157

Preparation of ethyl 3S-[[2-[[[3-[[[[(4-(aminosulfonyl)phenylmethyl]amino](cyanoimino)-methyl]amino]phenyl]carbonyl]amino]acetyl]-amino-4-pentynoate

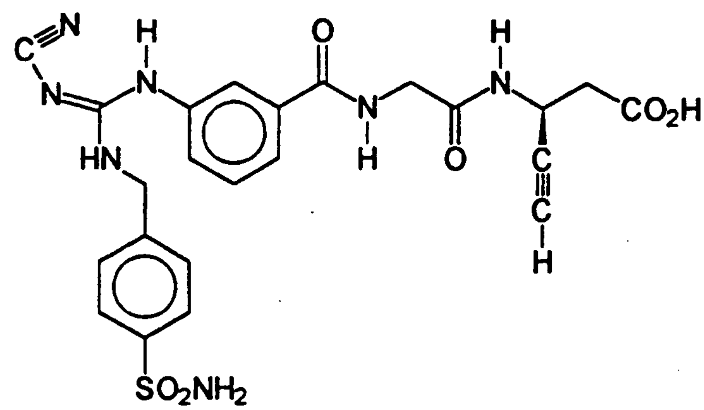


The title compound was prepared following the procedure described in Example 140, replacing the compound of Example J with that of Example AA. The above compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 158

Preparation of 3S-[[2-[[[3-[[[[(4-(aminosulfonyl)-phenylmethyl]amino](cyanoimino)methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]-4-pentynoic acid, trifluoroacetate salt, monohydrate



The above compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with that of Example 157. The crude product was purified by RPHPLC on a C18 column (eluant: 0.5% TFA-water/acetonitrile) and lyophilized to afford the title compound as a white solid.

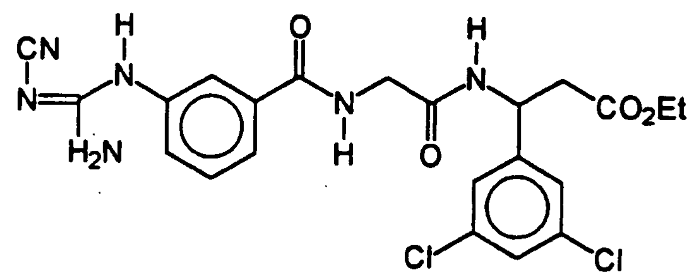
NMR was consistent with the proposed structure.

Analysis for $C_{23}H_{23}N_7O_6S$.1.25 TFA

Calculated:	C, 44.64; H, 3.86; N, 14.29.
Found:	C, 44.85; H, 4.00; N, 14.36.

EXAMPLE 159

Preparation of ethyl β-[[2-[[[3-[[amino(cyanoimino)-methyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-dichlorobenzenepropanoate

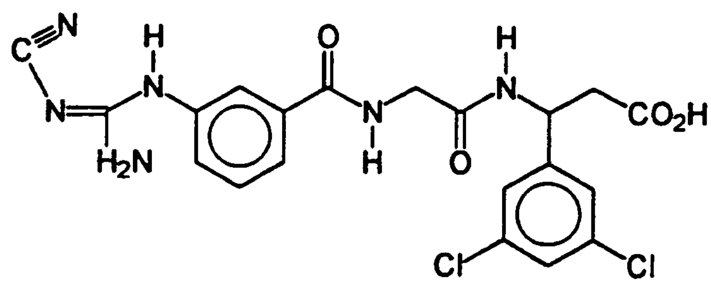


The title compound was prepared following the procedure described in Example 140, replacing the compound of Example J with that of Example K and replacing DL ethyl-β-[(2-amino-1-oxoethyl)amino]-4-pentynoate with compound of Example AD. The title compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 160

Preparation of β-[[2-[[[3-[[amino(cyanoimino)methyl]-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid

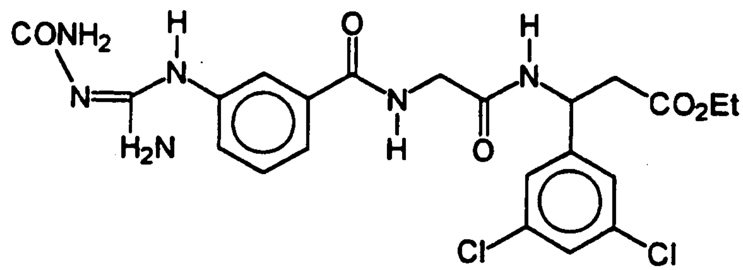


The title compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with that of Example 159. The crude product was purified by RHPLC on a C-18 column (eluant: 0.5% TFA/water/acetonitrile) and lyophilized to afford the title compound as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE 161

Preparation f ethyl β-[2-[[[3-[[amino(amin carbonyl)-imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt



To a stirred solution of Example 159 (2.65 g) in methylene chloride (120 ml) was added trifluoroacetic acid (60 ml). The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated *in vacuo* to afford crude product which upon crystallization from ether afforded the title compound (2.02 g) as a white solid.

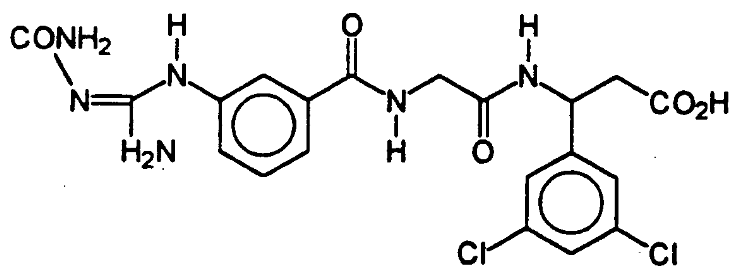
NMR was consistent with the proposed structure.

Analysis for $C_{21}H_{22}N_5O_4Cl_3$ 1.05 TFA.

Calculated:	C, 43.31; H, 3.79; N, 10.98.
Found:	C, 43.18; H, 3.81; N, 10.64.

EXAMPLE 162

Preparation of β-[[2-[[[3-[[amino(aminocarbonyl)imino]-methyl]amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt



The title compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with the compound of Example 161. The title compound was obtained as a white solid.

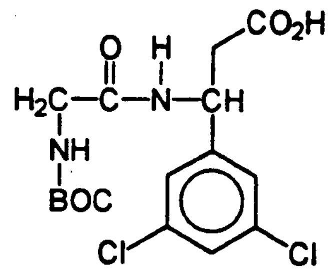
NMR was consistent with the proposed structure.

Analysis for $C_{20}H_{20}N_6O_5Cl_2$ 1.25 TFA:

Calculated:	C, 42.37; H, 3.36; N, 13.18.
Found:	C, 42.48; H, 3.46; N, 12.96.

EXAMPLE AE

Preparation of

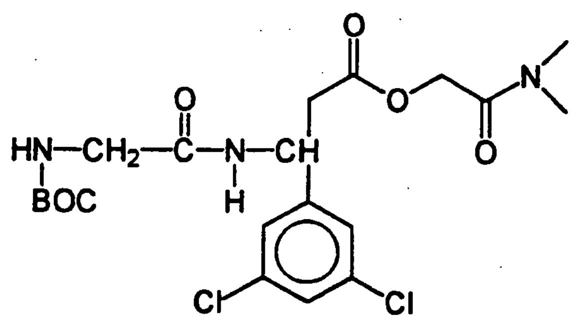


The title compound was prepared following the procedure described in Example 141 except that the compound of Example 140 was replaced with the compound of Example AC. The title compound was obtained as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE AF

Preparation of

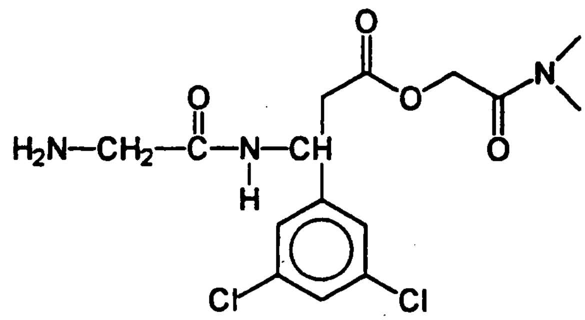


To a stirred solution of the compound of Example AE (954 mg, 33 mmol), DMF (10 ml), K_2CO_3 (1 g), NaI (129 mg) was added 363 mg of 2-chloro-N,N-dimethylacetamide (363 mg, 3 mmole) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* to afford an oily gum, which upon crystallization from diethylether yielded a white solid (AF) (610 mg).

NMR was consistent with the proposed structure.

EXAMPLE AG

Preparation of

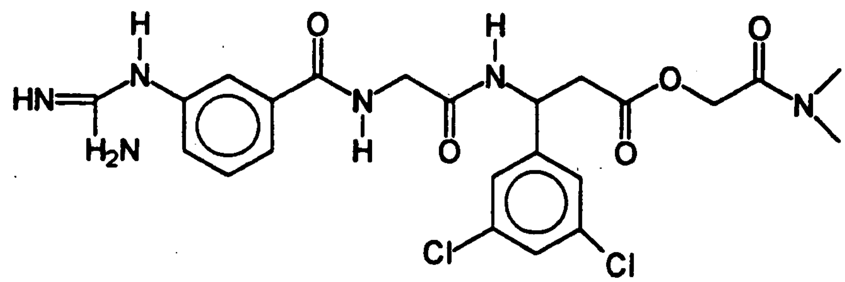


The title compound was prepared following the procedure described in Example 161, replacing the compound of Example 159 with the compound of Example AF. The title compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 163

Preparation of [(dimethylamino)carbonyl]methyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoate



The title compound was prepared following the procedure described in Example 132, replacing the compound of Example I with m-guanidino benzoic acid and replacing the compound of Example V with the compound of Example AG. The title compound was obtained as a white solid.

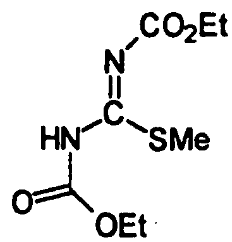
NMR was consistent with the proposed structure.

Analysis for $C_{23}H_{26}N_6O_3Cl_2$ 1.3 TFA:

Calculated:	C, 44.85; H, 4.01; N, 12.28
Found:	C, 44.51; H, 3.88; N, 12.38.

EXAMPLE AH

Preparation of

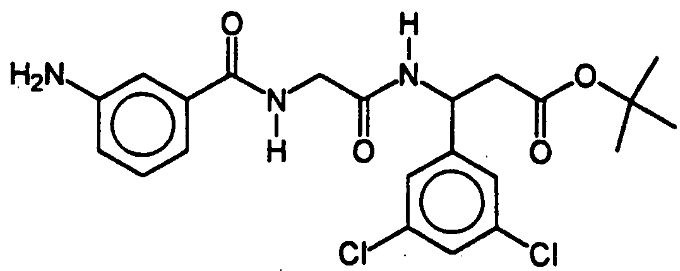


To a stirred solution of 2-methyl-2-thiopseudourea sulfate (11.1 g) in methylene chloride (150 ml) was added ethylchloroformate (8 ml) and saturated solution of sodium bicarbonate (150 ml). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude oily gum, which upon purification by flash column chromatography afforded the above compound (9.8 g) as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE 164

Preparation of

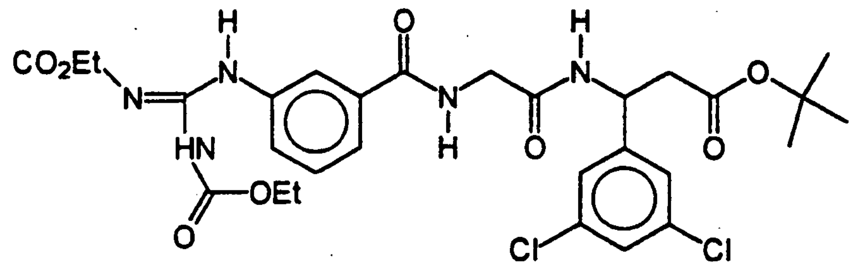


The title compound was prepared following the procedure described in Example 140, replacing the compound of Example J with 3-aminobenzoylglycine and replacing DL ethyl-β[(2-amino-1-oxoethyl)amino]-4-pentynoate with 3-amino-3-(3,5-dichlorophenyl)propionic acid tert-butyl ester. The title compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 165

Preparation of 1,1-dim thyl thyl 3,5-dichloro-β-[[2-[[[3-[[[(ethoxycarbonyl)amino][(ethoxycarbonyl)-imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoate

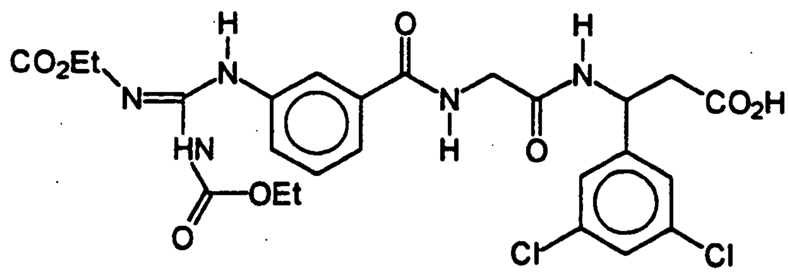


To a stirred solution of the compound of Example AH (250 mg) in DMF (2 ml), and triethylamine (150 mg) was added the compound of Example 164 (150 mg). The mixture was cooled to 0°C and stirred at 0°C for 5 minutes. The mixture was treated with $HgCl_2$ (50 mg), and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* to afford an oily gum which upon further purification by flash column chromatography yielded an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 166

Preparation of 3,5-dichloro-β-[[2-[[[3-[[[(ethoxycarbonyl)amino][(ethoxycarbonyl)-imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]benzenepropanoic acid



The title compound was prepared following the procedure described in Example 160, replacing the compound of Example 159 with the compound of Example 165. The title compound was obtained as a white solid.

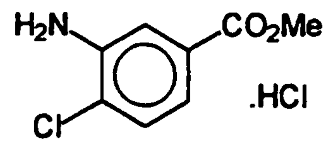
NMR was consistent with the proposed structure.

Analysis for $C_{25}H_{27}N_5O_8Cl_2$ 0.5 H_2O, 0.25 TFA:

Calculated:	C, 48.31; H, 4.49; N, 11.05.	
Found:	C, 48.55; H, 4.21; N, 10.84.	

EXAMPLE AI

Preparation of

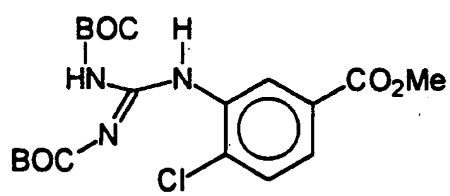


To a stirred suspension of 3-amino-4-chlorobenzoic acid (25.0 g, 157 mmol) in MeOH (300 ml) at 0°C, hydrogen chloride gas was added until the methanolic solution was saturated. The reaction mixture was stirred at 0-5°C for 30 minutes, allowed to attain room temperature, and then stirred for a further 4 days. The reaction mixture was concentrated *in vacuo* and the resulting white solid triturated with diethyl ether to afford the above compound; 26.2 g as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE AJ

Preparation of



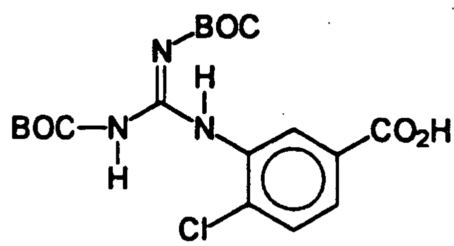
To a solution of bis-t-Boc-thiourea (24.8 g, 90 mmol) and methyl 3-amino-4-chlorobenzoate (20 g, 90 mmol) in dimethylformamide (120 ml) and triethylamine (45 ml) at 0°C, mercury (II) chloride (30.1 g, 111 mmol) was added. The reaction mixture was stirred for 15 minutes at 0°C, allowed to attain room temperature and stirred for a further 2 hours. The reaction mixture was diluted with ethyl acetate (600 ml) and the resulting slurry filtered

under reduced pressure. The filtrate was concentrated, to afford an oily gum which was purified by chromat graphy on silica (eluent: ethyl acetate/heptane 20:80) to afford the above compound (8.6 g) as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE AK

Preparation of

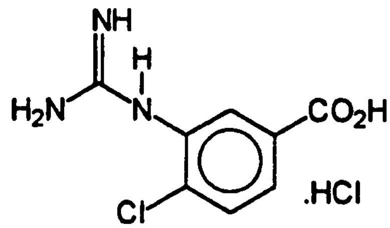


The product of Step AI was dissolved in MeOH (3 mL) and 1 M NaOH (14 mL) was added at room temperature. The reaction was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* and the residue dissolved in water, washed with ether. The aqueous layer was acidified to pH=3 with 1N HCl. A white precipitate formed, was filtered and washed with water and ether and dried to give 1.2 g of white solid.

NMR was consistent with the proposed structure.

EXAMPLE AL

Preparation of

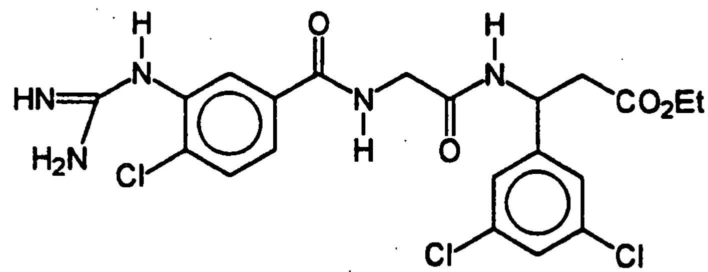


To a solution of the product of Step AJ (550 mg, 1.33 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL) at 0°C. The ice bath was removed after the addition and the reaction was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* to give a colorless oil. To this was added 4N HCl solution in dioxane (2 mL) and white precipitate formed. The solution was concentrated *in vacuo* to afford 280 mg of the desired product as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE 167

Preparation of ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]-4-chlorophenyl]carbonyl]amino]acetyl]-amino]3,5-dichlorobenzenepropanoate



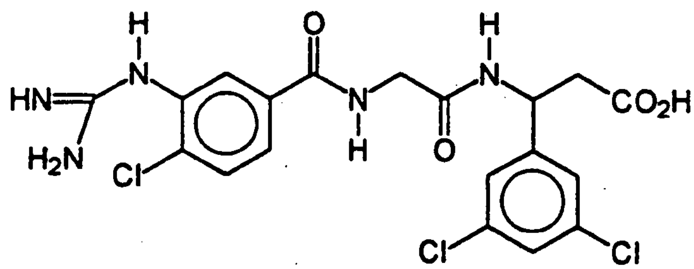
A solution of the compound of Example AL (500 mg) and 1-methylpiperidine (400 mg), in DMF (20 ml) was cooled to 0°C and isobutyl chloroformate (274 mg) was added under a nitrogen atmosphere. The reaction mixture was allowed to stir for 5 minutes before adding a solution of the compound of Example AD (866 mg) in DMF (2 ml). The reaction mixture was allowed to warm slowly to room temperature and was stirred at room temperature for 16 hours. The solution was quenched with water and extracted with ethyl acetate. The organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by RPHPLC and lyophilized to yield the desired product as an oily gum (329 mg).

Analysis for $C_{21}H_{22}N_5O_4Cl_3$ 1 TFA, 0.5 H_2O:

Calculated:	C, 43.31; H, 3.79; N, 10.98
Found:	C, 43.18; H, 3.81; N, 10.64.

EXAMPLE 168

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-4-chlorophenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt



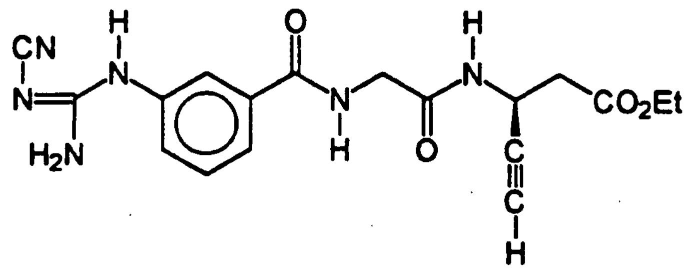
The title compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with that of Example 167. The title compound was obtained as a white solid. NMR was consistent with the proposed structure.

Analysis for $C_{19}H_{18}N_5O_4Cl_3$ • 1 TFA:

Calculated:	C, 41.98; H, 3.19; N, 11.66.
Found:	C, 42.14; H, 3.30; N, 11.18.

EXAMPLE 169

Preparation of



The title compound was prepared following the procedure described in Example 140, replacing the compound of Example J with that of Example K. The title compound was obtained as an oily gum.

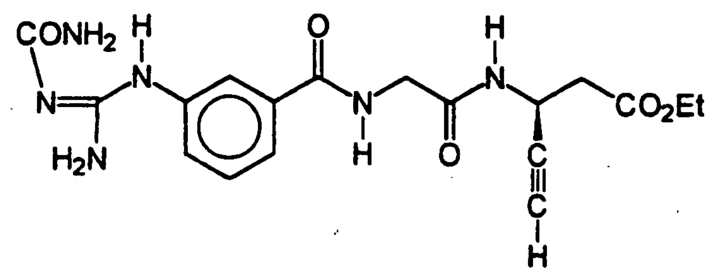
NMR was consistent with the proposed structure.

Analysis for $C_{18}H_{20}N_6O_4$ 0.6 TFA:

Calculated:	C, 50.93; H, 4.59; N, 18.56.
Found:	C, 50.69; H, 4.71; N, 18.32.

EXAMPLE 170

Preparati n of ethyl 3S-[[2-[[[3-[[amino-[(aminocarbonyl)imino]methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]-4-pentynoate

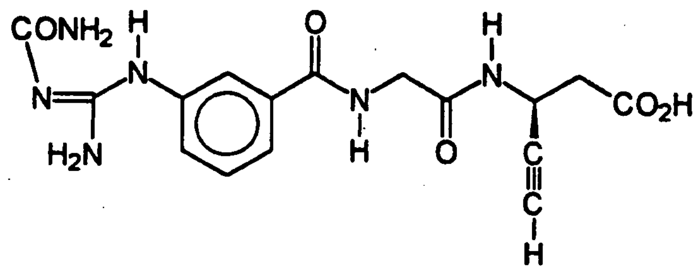


The title compound was prepared following the procedure described in Example 161, replacing the compound of Example 159 with that of Example 169. The title compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 171

Preparation of 3S-[[2-[[[3-[[amino[(aminocarbonyl)-imino]methyl]amino]phenyl]carbonyl]amino]-acetyl]amino]-4-pentynoic acid, trifluoroacetate salt, hydrate

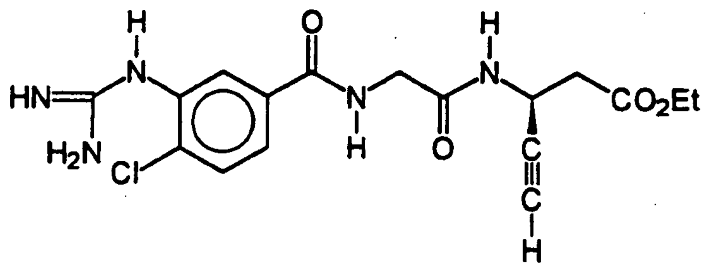


The title compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with the compound of Example 170. The title compound was obtained as a white solid.

NMR was consistent with the proposed structure.

EXAMPLE 172

Preparation of ethyl 3S-[[2-[[[3-[(aminoiminomethyl)-amino]-4-chlorophenyl]carbonyl]amino]-acetyl]amino]-4-pentynoate

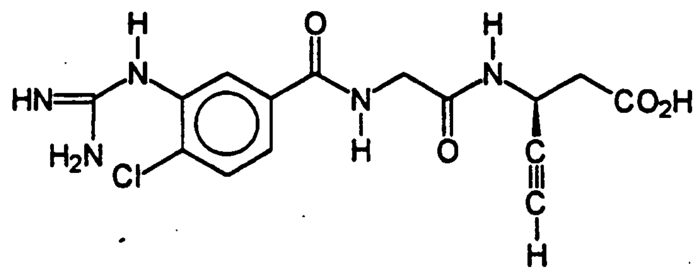


The title compound was prepared following the procedure described in Example 167, replacing the compound of Example AD with DL ethyl-β-[(2-amino-1-oxoethyl)amino]-4-pentynoate. The title compound was obtained as an oily gum.

NMR was consistent with the proposed structure.

EXAMPLE 173

Preparation of 3S-[[2-[[[3-[(aminoiminomethyl)-amino]-4-chlorophenyl]carbonyl]amino]acetyl]-amino]-4-pentynoic acid, trifluoroacetate salt



The title compound was prepared following the procedure described in Example 141, replacing the compound of Example 140 with the compound of Example 172. The title compound was obtained as a white solid.

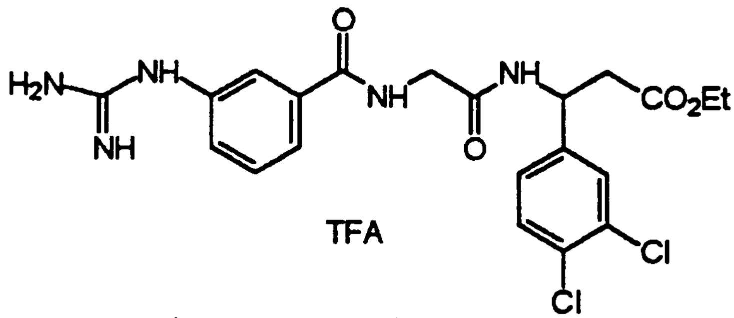
NMR was consistent with the proposed structure.

Analysis for $C_{15}H_{16}N_5O_4Cl$, 1 TFA, 0.5 H_2O:

Calculated:	C, 41.77; H, 3.71; N, 14.33.
Found:	C, 41.84; H, 3.64; N, 13.94.

EXAMPLE 174

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,4-dichlorobenzenepropanoate, trifluoroacetate salt



Step A

Ethyl-DL-3-amino-3-(3,4-dichlorophenyl)propionate hydrochloride was prepared according to Example 1, Steps A and B, substituting an equivalent amount of 3,4-dichlorobenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A.

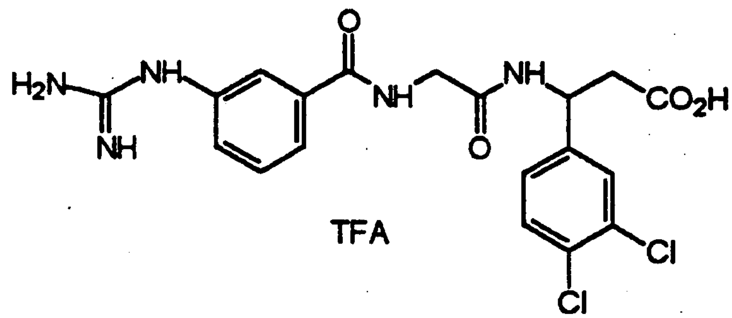
Step B

To m-guanidinohippuric acid hydrochloride (Example M) (400 mg, 0.0015 mole) and N-methylmorpholine (150 mg, 0.0015 mole) in anhydrous DMF (6 mL) was added, at ice bath temperature, isobutylchloroformate (200 mg, 0.0015 mole). After stirring for 5 minutes, a slurry of the product from Step A above (ethyl-DL-3-amino-3-(3,4-dichlorophenyl)propionate hydrochloride (440 mg, 0.0015 mole) and N-methylmorpholine (150 mg, 0.0015 mole) in anhydrous DMF (6 mL) was added in one portion at ice bath temperature. The reaction was stirred overnight at room temperature. The solvent was removed under vacuum on a 78°C water bath and the product was isolated by RPHPLC to yield the title compound (520 mg) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 175

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,4-dichlorobenzene-propanoic acid, trifluoroacetate salt

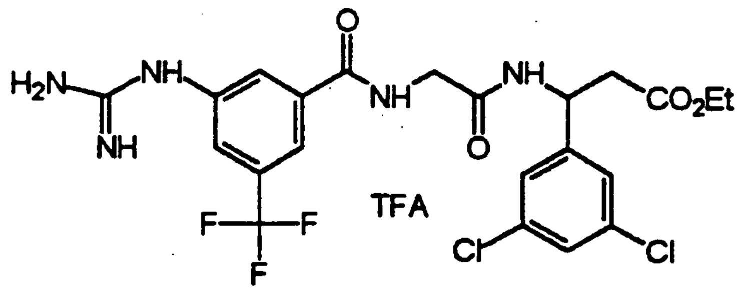


To the product from Example 174 (420 mg, 0.0007 mole) in H_2O (8 mL) and CH_3CN (8 mL) was added LiOH (118 mg, 0.003 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to ≃3 with TFA and the product was isolated by RPHPLC to yield the title compound (390 mg) (after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 176

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]-5-(trifluoromethyl)carbonyl]amino]acetyl]amino]-3,4-dichlorobenzenepropanoate, trifluoroacetate salt

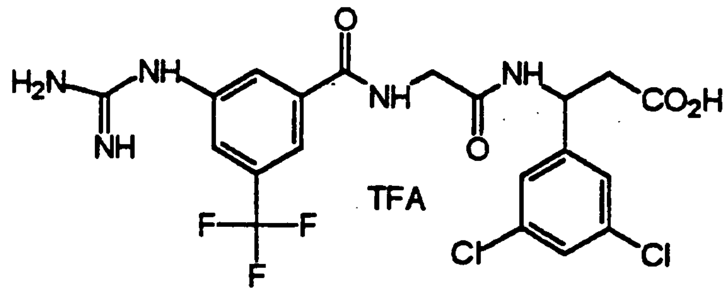


The above compound was prepared according to the methodology of Example 38, substituting the equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3,5-bis-trifluoromethylbenzaldehyde.

MS and NMR were consistent with the desired structure.

EXAMPLE 177

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt

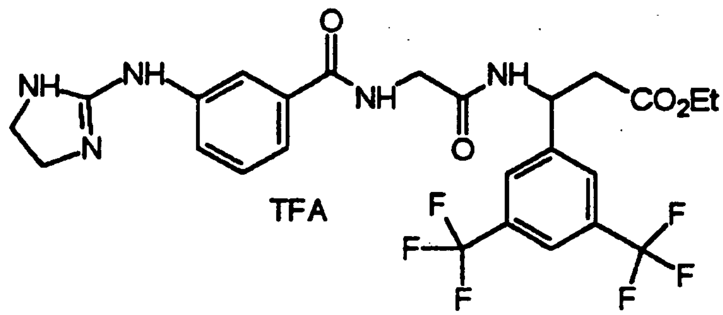


To the product from Example 176 (620 mg, 0.00094 mole) in H_2O (10 mL) and CH_3CN (10 mL) was added LiOH (157 mg, 0.0037 mole). The reaction mixture was stirred at room temperature for 2 hours. The pH was lowered to ~3 with TFA and the product was isolated by RPHPLC to yield the title compound (560 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 178

Preparation of (±) ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-bis(trifluoromethyl)benzenepropanoate, trifluoroacetate salt

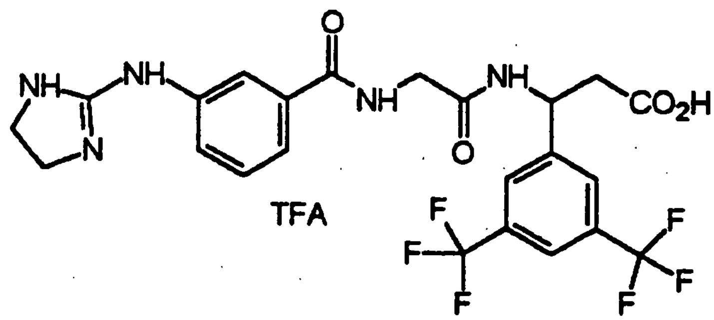


The above compound was prepared according to the methodology of Example 9, substituting the equivalent amount of 3,5-bis-trifluoromethylbenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A from Example 9, Step B.

MS and NMR were consistent with the desired structure.

EXAMPLE 179

Preparation of (±) β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-bis(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt

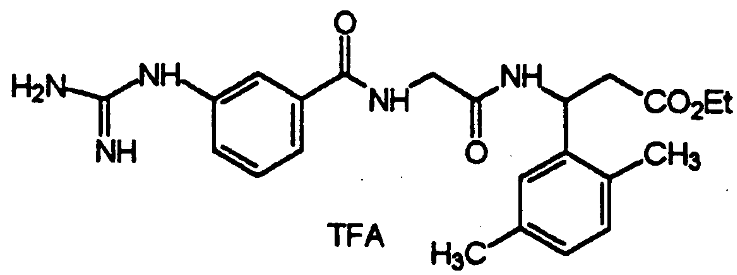


To the product from Example 178 (360 mg, 0.0005 mole) in H_2O (8 mL) and CH_3CN (8 mL) was added LiOH (88 mg, 0.0021 mole). The reaction was stirred at room temperature for 3 hours. The pH was lowered to ~3 with TFA and the product was isolated by RPHPLC to yield the title compound (300 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 180

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2,5-dimethylbenzenepropanoate, trifluoroacetate salt

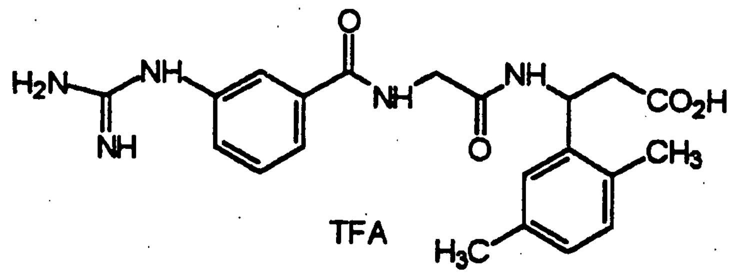


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 2,5-dimethylbenzaldehyde (Aldrich) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 181

Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2,5-dimethylbenzenepropanoic acid, trifluoroacetate salt

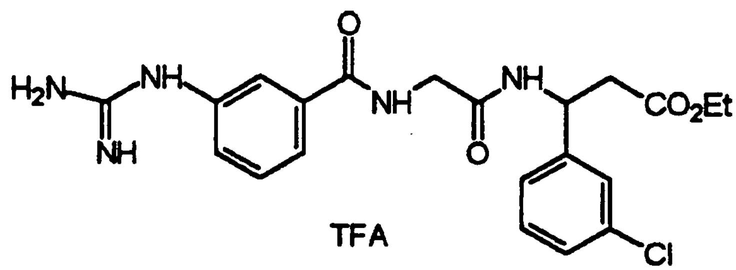


To the product from Example 180 (710 mg, 0.0013 mole) in H_2O (10 mL) and CH_3CN (10 mL) was added LiOH (215 mg, 0.005 mole). The reaction mixture was stirred at room temperature for 2.5 hours. The pH was lowered to ~3 with TFA and the product was isolated by RPHPLC to yield the title compound (600 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 182

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-chlorobenzenepropanoate, trifluoroacetate salt

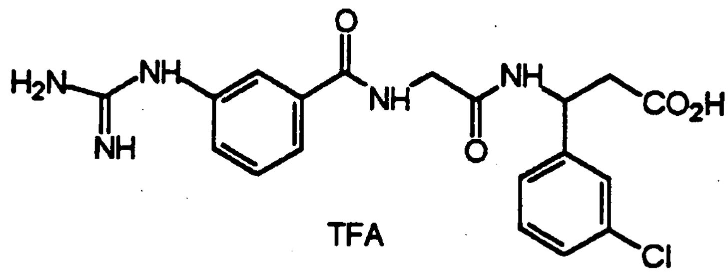


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 3-chlorobenzaldehyde (Aldrich) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 183

Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-chlorobenzenepropanoic acid, trifluoroacetate salt

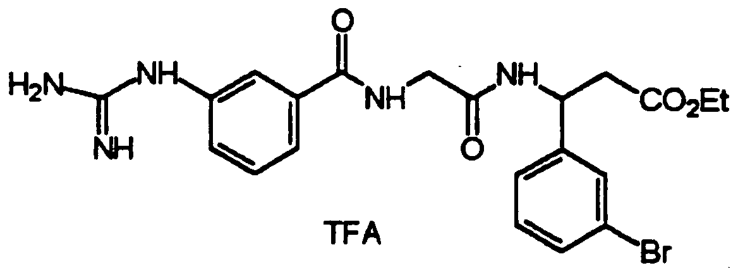


To the product from Example 182 (720 mg, 0.0013 mole) in H_2O (15 mL) and CH_3CN (10 mL) was added LiOH (880 mg, 0.02 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ≃2 with TFA and the product was isolated by RPHPLC to yield the title compound (550 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 184

Preparation f (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromobenzenepropanoate, trifluoroacetate salt

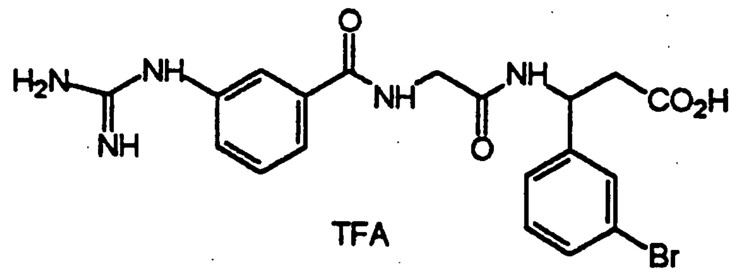


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 3-bromobenzaldehyde (Aldrich) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 185

Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromobenzenepropanoic acid, trifluoroacetate salt

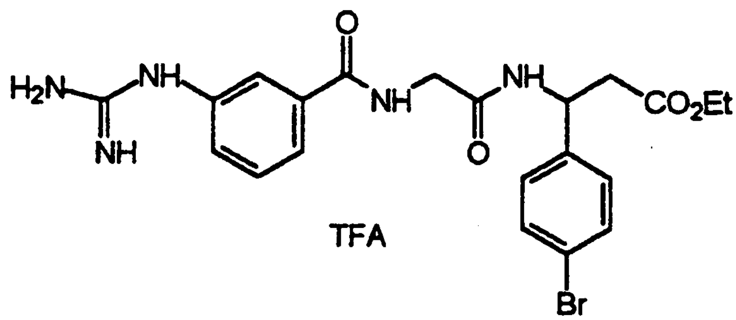


To the product from Example 184 (1.0 mg, 0.00165 mole) in H_2O (15 mL) and CH_3CN (10 mL) was added LiOH (210 mg, 0.005 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to ~2.5 with TFA and the product was isolated by RPHPLC to yield the title compound (460 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 186

Preparation f (±) ethyl β-[[2-[[[3-[(aminoimin methyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-bromobenzenepropanoate, trifluoroacetate salt

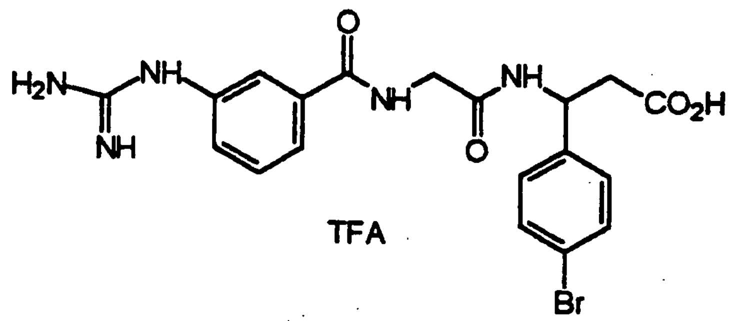


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 4-bromobenzaldehyde (Aldrich) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 187

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-bromobenzenepropanoic acid, trifluoroacetate salt

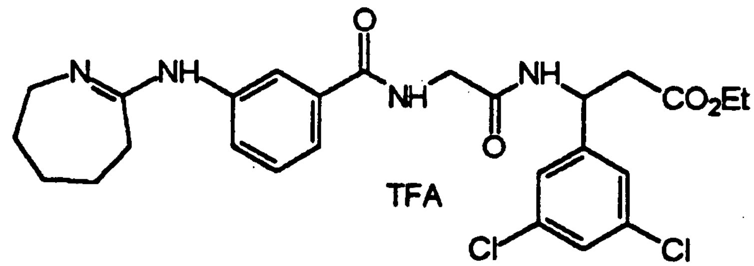


To the product from Example 186 (1.3 mg, 0.0023 mole) in H_2O (15 mL) and CH_3CN (15 mL) was added LiOH (290 mg, 0.0069 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to $\simeq$2.5 with TFA and the product was isolated by RPHPLC to yield the title compound (1.1 g after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 188

Preparation f (±) ethyl β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt

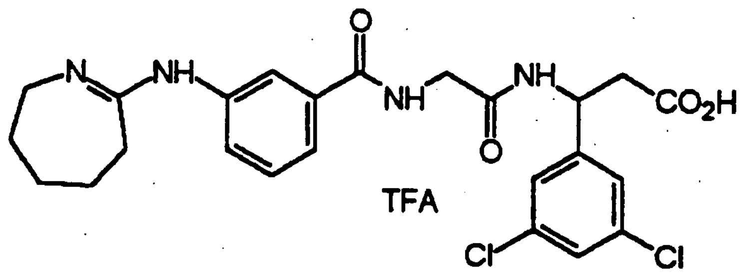


The above compound was prepared according to the methodology of Example 11, substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A from Example 11, Step B.

MS and NMR were consistent with the desired structure.

EXAMPLE 189

Preparation of (±) β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt

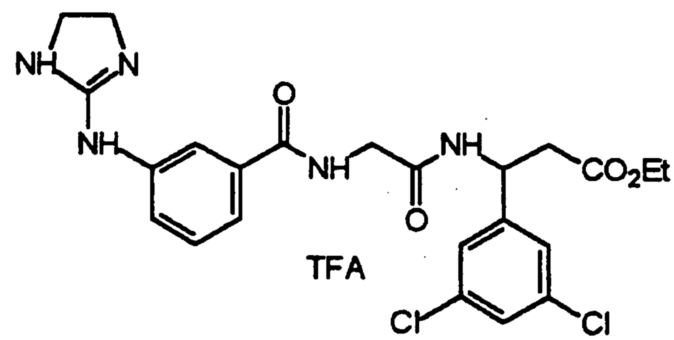


To the product from Example 188 (370 mg, 0.00057 mole) in H_2O (20 mL) and CH_3CN (15 mL) was added LiOH (192 mg, 0.0046 mole). The reaction mixture was stirred at room temperature for 3 hours. The pH was lowered to ~2.5 with TFA and the product was isolated by RPHPLC to yield the title compound (280 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 190

Preparation of (±) ethyl β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt

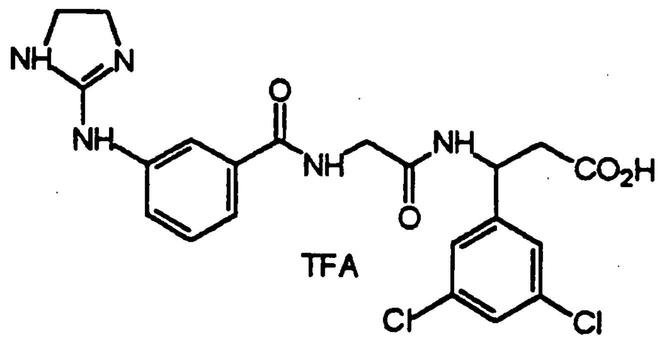


The above compound was prepared according to the methodology of Example 9, substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridinecarboxaldehyde in Example 1, Step A from Example 9, Step B.

MS and NMR were consistent with the desired structure.

EXAMPLE 191

Preparation of (±) β-[[2-[[[3-[(4,5-dihydro-1H-imidazol-2-yl)amino]phenyl]carbonyl]amino]-acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt

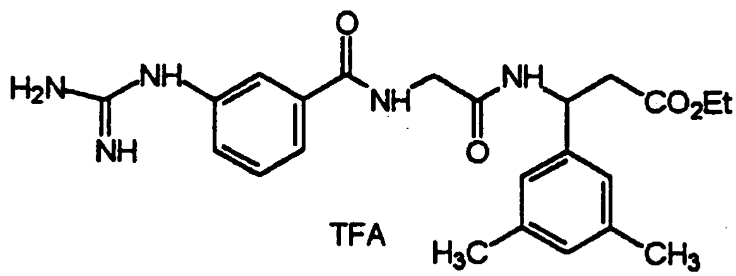


To the product from Example 190 (200 mg, 0.00032 mole) in H_2O (10 mL) and CH_3CN (10 mL) was added LiOH (54 mg, 0.0013 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to ≃2.5 with TFA and the product was isolated by RPHPLC to yield the title product (190 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 192

Preparation of (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dimethylbenzenepropanoate, trifluoroacetate salt

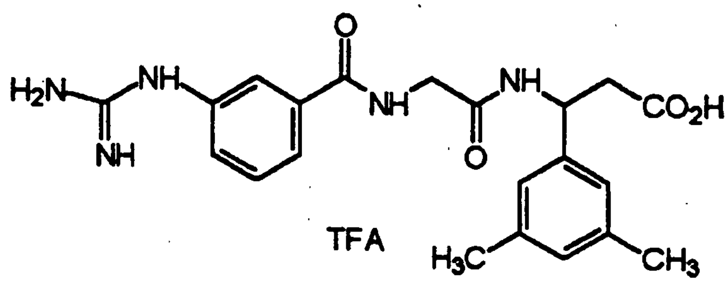


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 3,5-dimethylbenzaldehyde (Lancaster) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 193

Preparation of (±) β-[[2-[[[3-[(aminoimin methyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dimethylbenzenepropanoic acid, trifluoroacetate salt

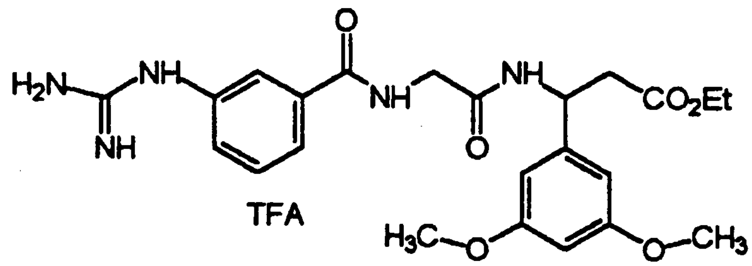


To the product from Example 192 (730 mg, 0.0013 mole) in H_2O (10 mL) and CH_3CN (10 mL) was added LiOH (221 mg, 0.005 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ~2.5 with TFA and the product was isolated by RPHPLC to yield the title compound (570 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 194

Preparation f (±) ethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dimethoxybenzenepropanoate, trifluoroacetate salt

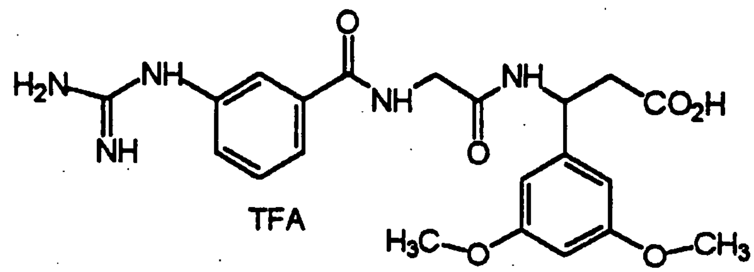


The above compound was prepared according to the methodology of Example 174, substituting an equivalent amount of 3,5-dimethoxybenzaldehyde (Aldrich) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 195

Preparati n of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dimethoxybenzenepropanoic acid, trifluoroacetate salt

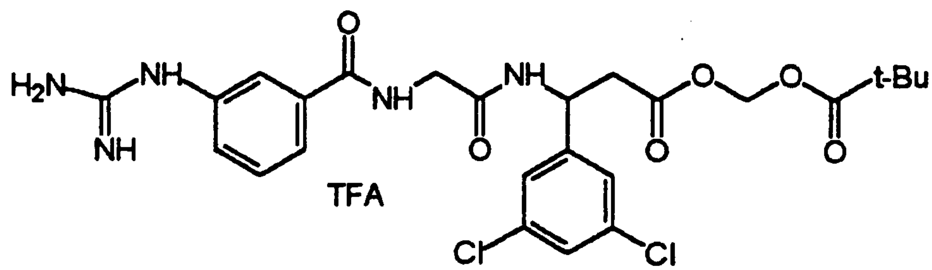


To the product from Example 194 (800 mg, 0.00014 mole) in H_2O (20 mL) and CH_3CN (8 mL) was added LiOH (230 mg, 0.0055 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to $\simeq$3 with TFA and the product was isolated by RPHPLC to yield the title compound (670 mg after lyophilization) as a white solid.

MS and NMR were consistent with the desired structure.

EXAMPLE 196

Preparation of (±) (2,2-dimethyl-1-oxopropoxy)methyl β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]carbonyl]-amino]acetyl]amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt



Step A

DL-3-amino-3-(3,5-dichlorophenyl)propionic acid was prepared according to the methodology of Example 1, Step A, substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridine carboxaldehyde in Example 1, Step A. MS and NMR were consistent with the desired structure.

Step B

To the product from Step A (3.0 g, 0.0128 mole) in dioxane (25 mL) and H_2O (13 mL) was added, at ice-bath temperature, NaOH (0.52 g, 0.013 mole) in H_2O (13 mL). After stirring at ice-bath temperature for 10 minutes, BOC anhydride (3.0 g, 0.014 mole) was added at ice-bath temperature. The reaction mixture was then stirred for 2 hours at room temperature. After the dioxane was removed under vacuum, the aqueous solution was cooled in an ice-bath and the pH was lowered to 2.5 with $KHSO_4$ after overlaying with ethyl acetate. The ethyl acetate layer was separated and the aqueous layer extracted twice more

with ethyl acetate. The combined ethyl acetate layers were washed with H_2O (3X), dri d over $MgSO_4$ and the solvent was rem ved under vacuum. The residue was slurried in 5% ethyl acetate/hexane overnight resulting in a white solid. This was filtered, washed with 10% ethyl acetate/hexane and dried to yield N-BOC-DL-3-amino-3-(3,5-dichlorophenyl)-propionic acid (2.9 g) as a white solid.

Step C

To the product from Step B (2.5 g, 0.0075 mole) in acetone (30 mL) and H_2O (5 mL) was added KOH (87%) (0.5 g, 0.0075 mole). To this was added chloromethyl pivalate (1.3 g, 0.0084 mole) (Aldrich), followed by NaI (190 mg). The reaction mixture was stirred overnight at reflux. The solvent was removed under vacuum. The residue was taken up in ether. The ether was washed with saturated $NaHCO_3$ (2X), H_2O (3X), dried over $MgSO_4$ and removed under vacuum to yield pivaloyloxymethyl N-BOC-DL-3-amino-3-(3,5-dichlorophenyl)propionate (2.92 g) as a white solid. MS and NMR were consistent with the desired structure.

Step D

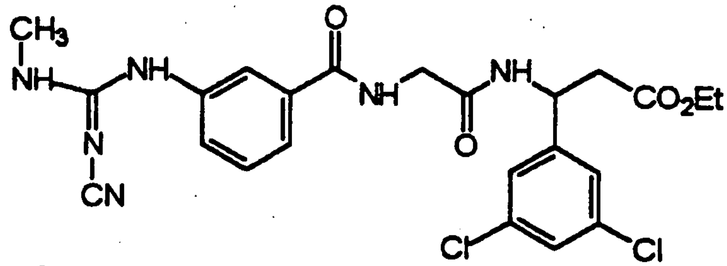
To the product from Step C (2.92 g, 0.0065 mole) was added excess 4M HCl in dioxane (Aldrich). The reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum and the residue was slurried 2X with petroleum ether/isopropyl ether (50:50) and 1X with petroleum ether (the solvents are decanted off each time). The resulting solid was dried under vacuum to yield pivaloyloxymethyl DL-3-amino-3-(3,5-dichlorophenyl)propionate hydrochloride (2.0 g) as a white solid. MS and NMR were consistent with the desired structure.

Step E

The title comp und was prepared according to the m thodol gy f Example 174, Step B, substituting an equivalent amount of the product from Step D above for the product from Example 174, Step A in Example 174, Step B. The title compound was isolated as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 197

Preparation of (±) ethyl 3,5-dichloro-β-[[2-[[[3-[(cyanoimino)(methylamino)methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoate



Step A

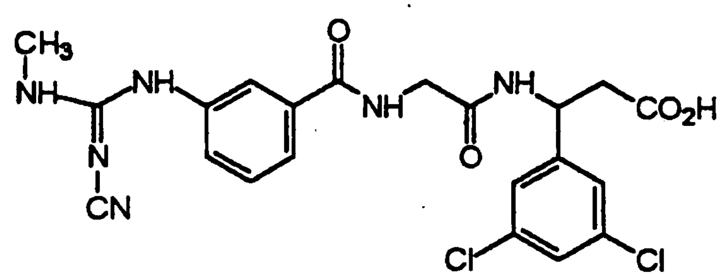
Ethyl β-[(2-aminoacetyl)amino](3,5-dichlorophenyl)-3-propanoate hydrochloride was prepared according to the methodology of Example 1, Steps A-D, substituting an equivalent amount of 3,5-dichlorobenzaldehyde for 3-pyridinecarboxaldehyde in Example 1, Step A. MS and NMR were consistent with the desired structure.

Step B

To the product from Step A above (1.1 g, 0.0031 mole), the product from Example J (680 mg, 0.0031 mole), DMAP (38 mg, 0.00031 mole), triethylamine (320 mg, 0.0031 mole) and methylene chloride (12 mL) was added, at ice-bath temperature, EDCI (600 mg, 0.0031 mole). The reaction mixture was stirred at ice-bath temperature for 15 minutes then at room temperature overnight. After removing the solvent under vacuum, the residue was taken up in ethyl acetate. The ethyl acetate was washed with saturated $NaHCO_3$ (1X), H_2O (2X), dried over $MgSO_4$ then removed under vacuum. The resulting solid was slurried in ethyl acetate:isopropyl ether (1:3) for 1 hour. The resulting solid was filtered, washed with isopropyl ether and dried under vacuum to yield the title compound (1.35 g) as a white solid.

EXAMPLE 198

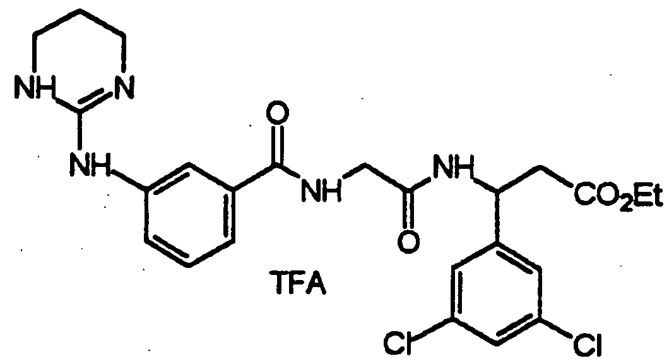
Preparation of (±) 3,5-dichloro-β-[[2-[[[3-[(cyanoimino)(methylamino)methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid



To the product from Example 197, Step B (1.18 g, 0.0023 mole) in H_2O (15 mL) and CH_3CN (15 mL) was added LiOH (240 mg, 0.0057 mole). The reaction mixture was stirred at room temperature for 3 hours. The pH was lowered to $\simeq$3 with TFA and the product was isolated by RPHPLC to yield the title compound (1.02 g after lyophilization) as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 199

Preparation of (±) ethyl 3,5-dichloro-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoate, trifluoroacetate salt



Step A

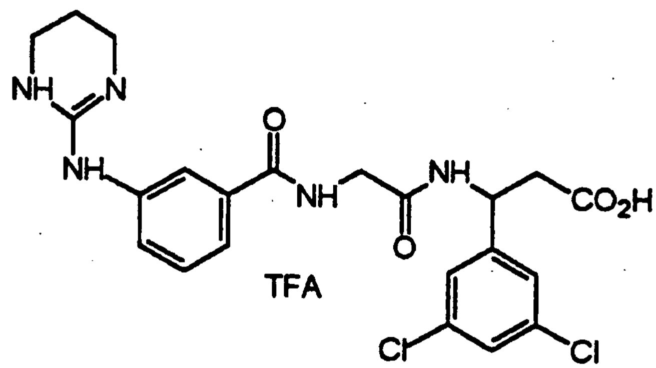
To the product from Example 23, Step A (10.1 g, 0.03 mole) in DMF (15 mL) was added 1,3-diaminopropane (2.3 g, 0.031 mole), triethylamine (3.9 g, 0.03 mole) and DMAP (420 mg). The reaction mixture was heated at 140-150°C for 4.5 hours (thick precipitate). After cooling to room temperature, H_2O (30 mL) was added and, after stirring for 15 minutes, the precipitate was filtered and washed with H_2O. This precipitate was slurried in H_2O and made acidic with concentrated HCl. A solution formed. After lyophilizing off the solvent, the residue was slurried 2X with isopropyl ether (which was decanted off each time). After drying under vacuum, the yield of 3-(2-amino-1,4,5,6-tetrahydropyrimidine)benzoic acid hydrochloride was 4.0 g as a white solid. MS and NMR were consistent with the desired structure.

Step B

To the product from Step A above (884 mg, 0.0035 mole) and NMM (350 mg, 0.0035 mole) in anhydr us DMF (6 mL) was added, at ice-bath temperature, isobutylchloroformate (470 mg, 0.0035 mole). After stirring for 5 minutes, a slurry of the product from Example 197, Step A (1.07 g, 0.003 mole) and NMM (300 mg, 0.003 mole) in anhydrous DMF (6 mL) was added at ice-bath temperature. The solution was stirred overnight at room temperature. The solvent was removed under vacuum and the product was isolated by RPHPLC to yield the title compound (820 mg after lyophilization) as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 200

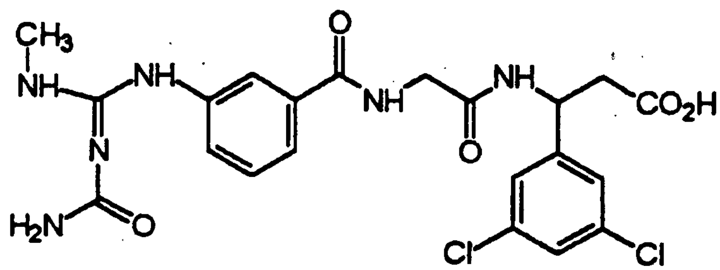
Preparati n of (±) 3,5-dichloro-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt



To the product from Example 199, Step B (780 mg, 0.0012 mole) in H_2O (10 mL) and CH_3CN (10 mL) was added LiOH (830 mg, 0.005 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to ~2.5 with TFA and the product was isolated by RPHPLC to yield the title compound (560 mg after lyophilization) as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 201

Preparation of (±) β-[[2-[[[3-[[[(aminocarbonyl)-imino)methylamino)methyl]amino]phenyl]-carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid

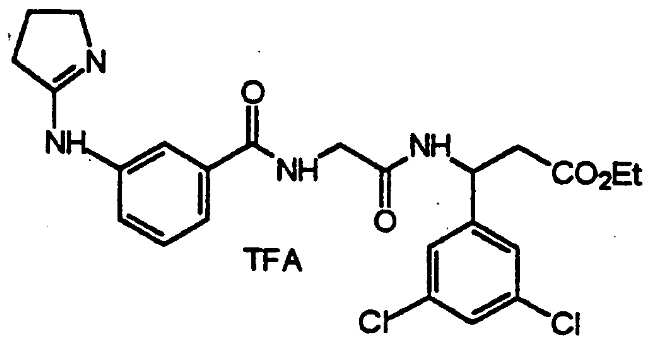


To the product from Example 198 (300 mg, 0.0006 mole) in CH_3CN (10 mL) and H_2O (25 mL) was added TFA (6 mL). The reaction mixture was stirred at room temperature for 2 weeks. The product was isolated by RPHPLC to yield the title compound (290 mg after lyophilization) as a white solid.

MS and NMR was consistent with the desired structure.

EXAMPLE 202

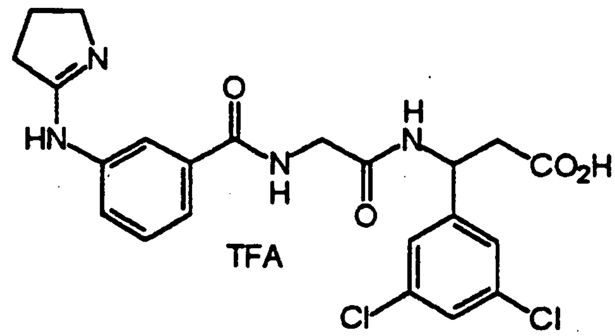
Preparation of (±) ethyl β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 16, substituting an equivalent amount of 3,5-dichlorobenzaldehyde (Aldrich) for 3-pyridine carboxaldehyde in Example 1, Step A, which was used to synthesize the product from Example 1, Step D, used in Example 11, Step B. MS and NMR were consistent with the desired structure.

EXAMPLE 203

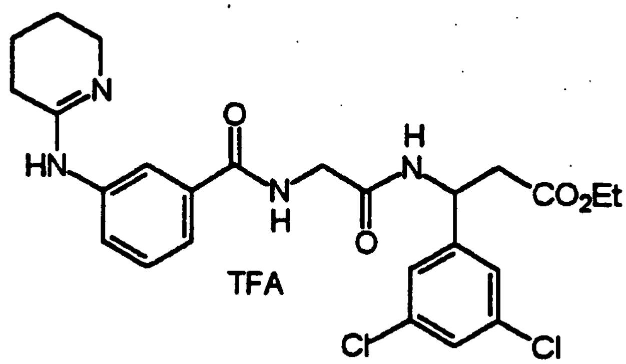
Preparation of (±) β-[[2-[[[3-[(3,4-dihydro-2H-pyrrol-5-yl)amino]phenyl]carbonyl]amino]acetyl]-amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt



To the product from Example 202 (1.27 g, 0.002 mole) in H_2O (15 mL) and CH_3CN (15 mL) was added LiOH (345 mg, 0.0082 mole). The reaction mixture was stirred at room temperature for 1.5 hours. The pH was lowered to 2.7 with TFA and the product was isolated by RPHPLC to yield the title compound (80 mg after lyophilization) as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 204

Preparation of (±) ethyl 3,5-dichl ro-β-[[2-[[[3-[(2,3,4,5-tetrahydropyridin-6-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoate, trifluoroacetate salt



Step A

To O-methylvalerolactim (Oakwood) (6.9 g, 0.061 mole) in CH_3CN (75 mL) was added 3-aminobenzoic acid, hydrochloride (Aldrich) (10 g, 0.0576 mole). After briefly heating to form a solution, the reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered, washed with CH_3CN and dried under vacuum to yield 3-(1-aza-2-amino-1-cyclohexene)benzoic acid hydrochloride (12.2 g) as a white solid. MS and NMR were consistent with the desired structure.

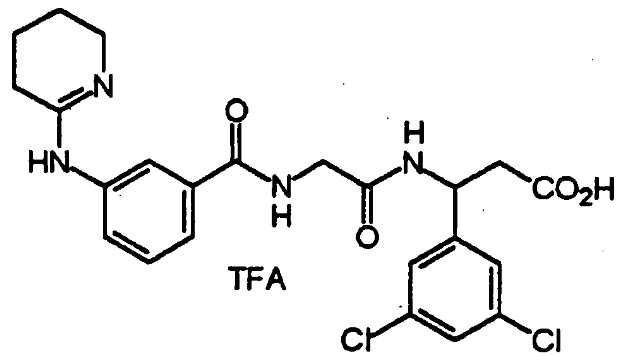
Step B

The title compound was prepared according to the methodology of Example 199, substituting an equivalent amount of the product from Step A above, for the product from Example 199, Step A in Example 199, Step B.

MS and NMR were consistent with the desired structure.

EXAMPLE 205

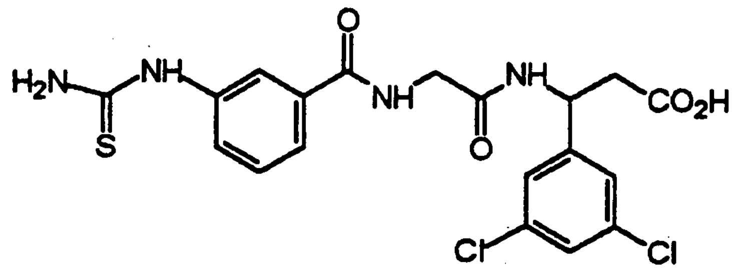
Preparation f (±) 3,5-dichloro-β-[[2-[[[3-[(2,3,4,5-tetrahydropyridin-6-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt



To the product from Example 204, Step B (890 mg, 0.0014 mole) in H_2O (20 mL) and CH_3CN (20 mL) was added LiOH (236 mg, 0.0056 mole). The reaction mixture was stirred at room temperature for 1 hour. The pH was lowered to ~3 with TFA and the product was isolated by RPHPLC to yield the title compound (320 mg after lyophilization) as a white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 206

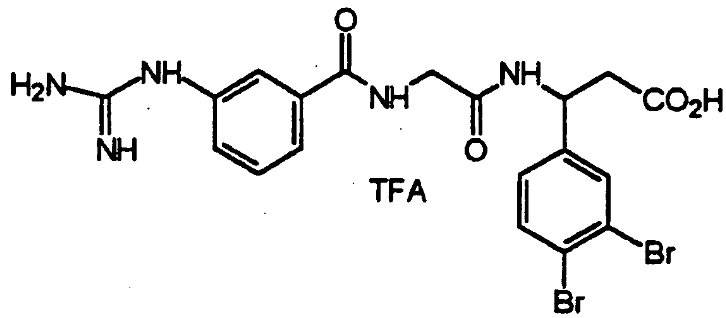
Preparation f (±) β-[[2-[[[3-[(aminothioxomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoic acid



The above compound was prepared according to the methodology of Example 198, substituting an equivalent amount of 1-(3-carboxyphenyl)-2-thiourea (Transworld) for the product from Example J in Example 197, Step B. MS and NMR were consistent with the desired structure.

EXAMPLE 207

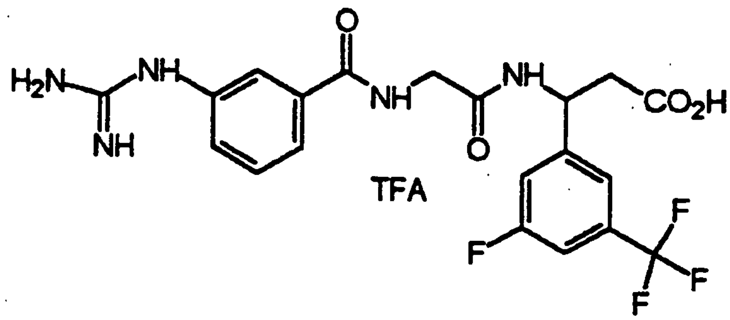
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,4-dibromobenzenepropanoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 175, substituting an equivalent amount of 3,4-dibromobenzaldehyde (Lancaster) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 208

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-fluoro-5-(trifluoromethyl)benzenepropanoic acid, trifluoroacetate salt

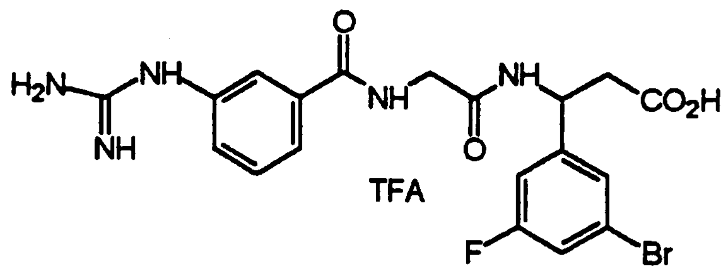


The above compound was prepared according to the methodology of Example 175, substituting an equivalent amount of 3-fluoro-5-trifluoromethylbenzaldehyde (Lancaster) for 3,4-dichlorobenzaldehyde in Example 174, Step A.

MS and NMR were consistent with the desired structure.

EXAMPLE 209

Preparation of (±) β-[[2-[[[3-[(aminoimin methyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromo-5-fluorobenzenepropanoic acid, trifluoroacetate salt



Step A

To 1-fluoro-3,5-dibromobenzene (Lancaster) (10 g, 0.0394 mole) in anhydrous ethyl ether (50 mL), in a flame dried flask under N_2 and at -78°C was added 1.6 m butyl lithium in hexane (Aldrich) dropwise, keeping the temperature below -78°C during the addition. After the addition was complete, the reaction was stirred at -78°C for an additional 50 minutes. The reaction was slowly warmed to -30°C, then andhyrous DMF (3.6 g, 0.049 mole) was added dropwise and at such a rate as to keep the temperature below -20°C.

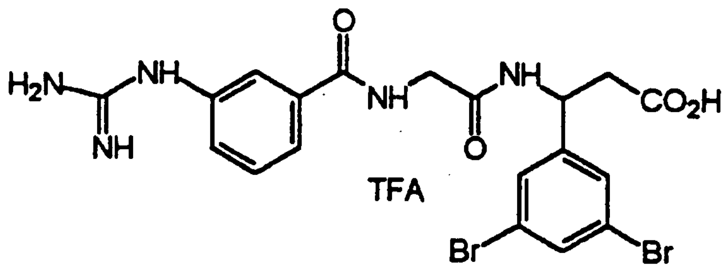
After the addition was complete, the temperature was slowly raised to 0°C over an hour, then stirred overnight at room temperature. The reaction mixture was slowly poured into cold 10% aqueous HCl (80 mL). After stirring for 15 minutes, the ether layer was separated and the ether was washed with H_2O (4X), dried over $MgSO_4$ and removed under vacuum to yield 3-bromo-5-fluorobenzaldehyde (8.16 g) as an amber liquid. MS and NMR were consistent with the desired product.

Step B

The title compound was prepar d according to the methodology of Example 175, substituting an equivalent amount of 3-bromo-5-fluorobenzaldehyde (Step A above) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 210

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dibromobenzenepropanoic acid, trifluoroacetate salt



Step A

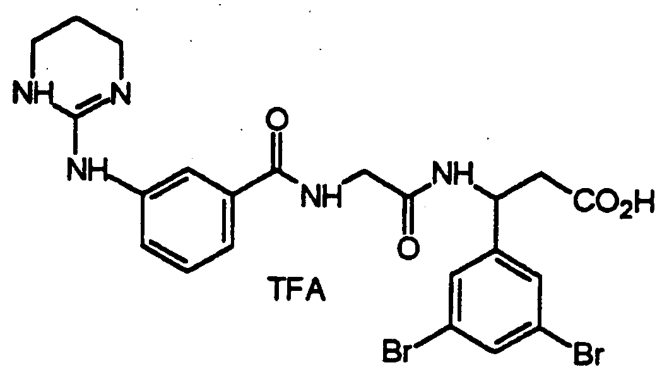
To 3,5-dibromobenzylbromide (Lancaster) (20 g, 0.061 mole) in H_2O (27 mL) and glacial acetic acid (27 mL) was added hexamethylenetetramine (Aldrich). The reaction mixture was heated at reflux for 2 hours. Concentrated HCl (22 mL) was then added and the refluxing was continued for 30 minutes. After cooling to room temperature, the reaction mixture was poured into H_2O (230 mL) and stirred for 10 minutes. The resulting precipitate was filtered, washed with H_2O and dried to yield 3,5-dibromobenzaldehyde (11.45 g) as a white solid. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 175, substituting an equivalent amount of 3,5-dibromobenzaldehyde (Step A above) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 211

Preparation of (±) 3,5-dibromo-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt



Step A

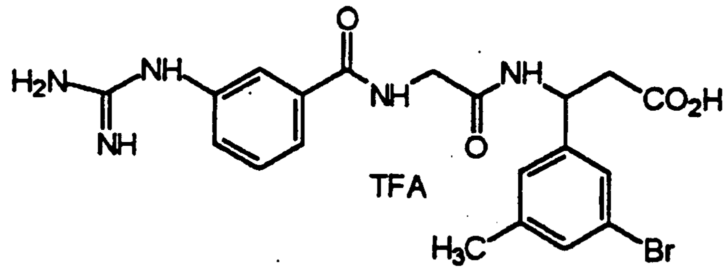
Ethyl-β-[(2-aminoacetyl)amino](3,5-dibromophenyl)-3-propanoate hydrochloride was prepared according to the methodology of Example 1, Steps A-D, substituting an equivalent amount of 3,5-dibromobenzaldehyde (Example 210, Step A) for 3-pyridinecarboxaldehyde in Example 1, Step A. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 200, substituting an equivalent amount of the product from Example 211, Step A (above) for the product from Example 197, Step A in Example 199, Step B. MS and NMR were consistent with the desired structure.

EXAMPLE 212

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromo-5-methylbenzenepropanoic acid, trifluoroacetate salt



Step A

To 5-bromo-m-xylene (24.03 g, 0.13 mole) in benzene (125 mL) was added benzoylperoxide (3.04 g, 0.013 mole). The reaction mixture was heated to reflux in a 250 mL round bottom flask. N-bromosuccinimide (18.15 g, 0.10 mole) was added in portions over 15 minutes. After 2 hours, heating was discontinued and the reaction mixture was allowed to cool to room temperature. Precipitated solids were removed by filtration and the filtrate was concentrated. The residue was taken up in hexane and additional solids were removed by filtration. The filtrate was passed through a small pad of silica gel and the filtrate was concentrated. The resultant yellow oil was titurated with MeOH over ice to give 3-bromo-5-methylbenzyl bromide (7.34 g) as a white solid. MS and NMR were consistent with the desired structure.

Step B

To 3-bromo-5-methylbenzyl bromide (Step A above) (5.49 g, 20 mmole) in glacial acetic acid (9.0 mL) and H_2O (9 mL) was added hexamethylenetetramine (4.50 g, 32 mmole) and th reaction was stirred at reflux for 2 hours.

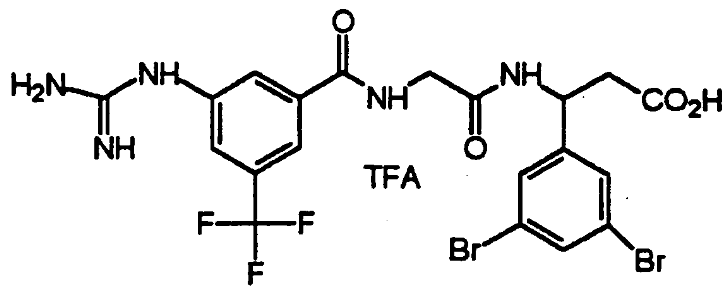
Concentrated HCl (7.0 mL) was added and the mixtur was refluxed an additional 15 minutes. After cooling to room temperature, the reaction mixtur was dilut d with H_2O (75 mL) and extracted with ether (150 mL). The ether layer was washed with H_2O (3 X 25 mL), 10% $NaHCO_3$ (2 X 50 mL) and dried over $MgSO_4$. The ether was removed under vacuum and the residue was chromatographed on silica gel eluting with hexane and 10% Et_2O/hexane to yield 3-bromo-5-methylbenzaldehyde (2.80 g) as a light yellow oil which solidified upon standing. MS and NMR were consistent with the desired structure.

Step C

The title compound was prepared according to the methodology of Example 175 substituting an equivalent amount of 3-bromo-5-methylbenzaldehyde (Step B above) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 213

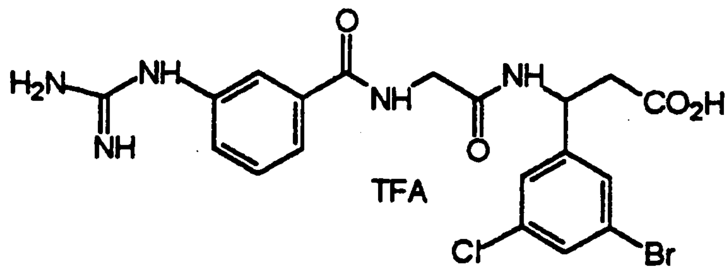
Preparati n of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]-acetyl]amino]-3,5-dibromobenzenepropanoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 39, substituting the equivalent amount of 3,5-dibromobenzaldehyde (Example 210, Step A) for 3,5-bis-trifluoromethylbenzaldehyde in Example 38. MS and NMR were consistent with the desired structure.

EXAMPLE 214

Preparation of (±) β-[[2-[[[3-[(aminoiminom thyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromo-5-chlorobenzenepropanoic acid, trifluoroacetate salt



Step A

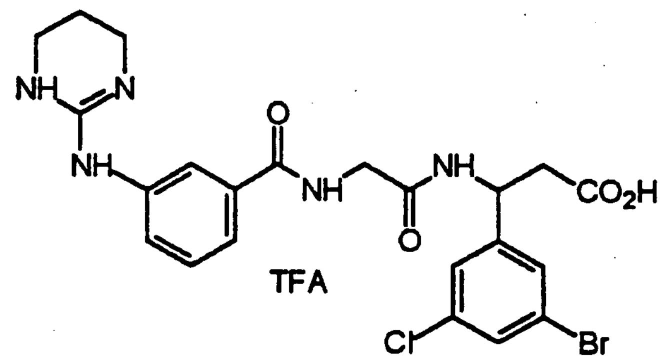
To 1-chloro-3,5-dibromobenzene (Esprit) (20 g, 0.074 mole) in anhydrous ethyl ether (150 mL) in a flame dried flask under N_2 and at -78°C was added 1.6 m butyl lithium in hexane dropwise, keeping the temperature below -78°C, then warmed to -30°C. Anhydrous DMF (6.8 g, 0.092 mole) was added dropwise, keeping the temperature below -20°C. After the addition was complete, the reaction was slowly warmed to 0°C, then stirred overnight at room temperature. The reaction mixture was poured slowly into chilled 10% aqueous HCl (160 mL). After stirring for 15 minutes, the ether was separated, washed with H_2O (4X), dried over $MgSO_4$ and removed under vacuum to yield 3-bromo-5-chlorobenzaldehyde (13 g) as a white solid. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 175, substituting an equivalent amount of 3-bromo-5-chlorobenzaldehyde (Step A above) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 215

Preparation of (±) 3-bromo-5-chloro-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt



Step A

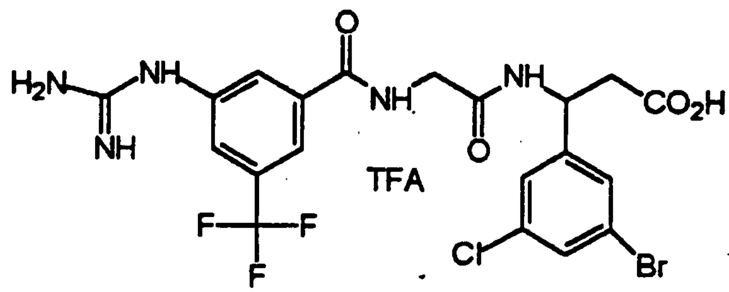
Ethyl β-[(2-aminoacetyl)amino](3-bromo-5-chlorophenyl)-3-propanoate hydrochloride was prepared according to the methodology of Example 1, Steps A-D, substituting an equivalent amount of 3-bromo-5-chlorobenzaldehyde (Example 214, Step A) for 3-pyridinecarboxaldehyde in Example 1, Step A. MS and NMR were consistent with the desired structure.

Step B

The title compound was prepared according to the methodology of Example 200, substituting an equivalent amount of the product from Step A (above) for the product from Example 197, Step A in Example 199, Step B. MS and NMR were consistent with the desired structure.

EXAMPLE 216

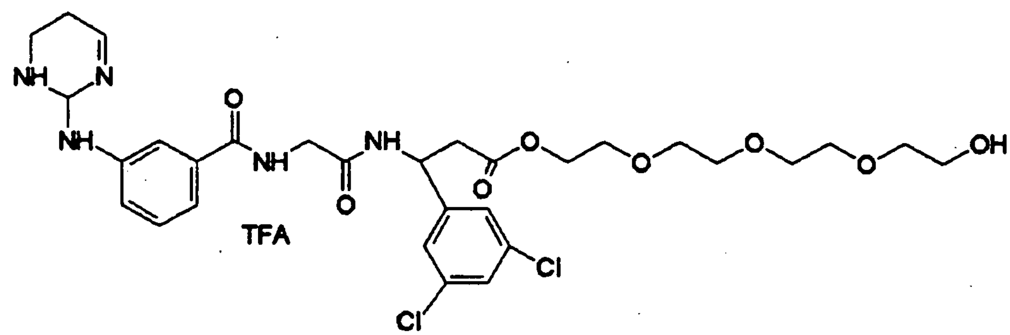
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]-5-(trifluoromethyl)phenyl]carbonyl]amino]-acetyl]amino]-3-bromo-5-chlorobenzenepropanoic acid, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 39, substituting an equivalent amount of 3-bromo-5-chlorobenzaldehyde (Example 214, Step A) for 3,5-bis-trifluoromethylbenzaldehyde in Example 38. MS and NMR were consistent with the desired structure.

EXAMPLE 217

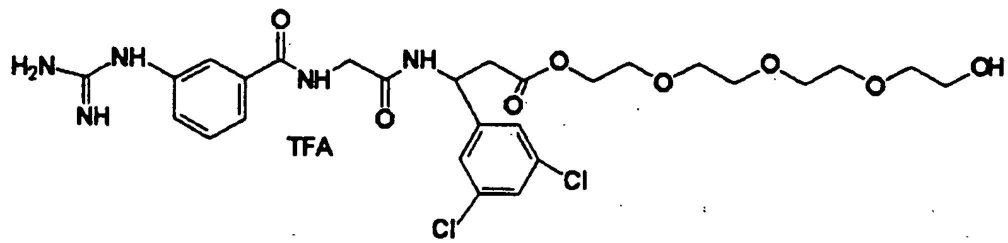
Preparati n of (±) [2-[2-[2-(2-hydroxyethoxy)-ethoxy]ethoxy]ethyl] 3,5-dichloro-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoate, trifluoroacetate salt



To the product of Example 200 (200 mg, 0.00033 mole) in DMA (1.5 mL) was added carbonyldiimidazole (67 mg, 0.00041 mole). The reaction was stirred at room temperature for 1 hour. Tetraethyleneglycol (214 mg, 0.0011 mole) was then added and the reaction mixture was stirred overnight at 60°C. The reaction was cooled to room temperature and the product was isolated by RPHPLC to yield the title compound (120 mg after lyophilization) as a hygroscopic white solid. MS and NMR were consistent with the desired structure.

EXAMPLE 218

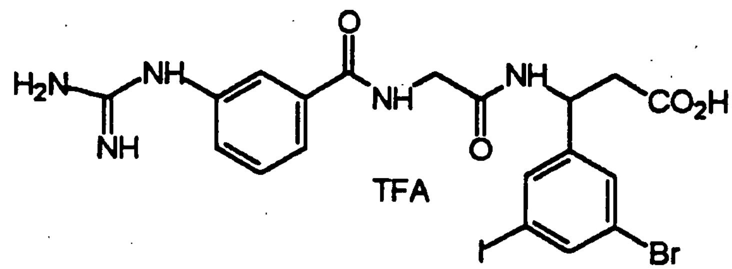
Preparation of (±) [2-[2-[2-(2-hydroxyethoxy)-ethoxy]ethoxy]ethyl] β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dichlorobenzenepropanoate, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 217, substituting an equivalent amount of the product of Example 27, for the product of Example 200. MS and NMR were consistent with the desired structure.

EXAMPLE 219

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromo-5-iodobenzenepropanoic acid trifluoroacetate salt



Step A

Methanol (40 mL) was added to a 250 mL round bottom flask followed by 60 mL of a solution saturated with anhydrous hydrochloric acid. 3-bromo-5-iodobenzoic acid (Aldrich)(5.02 g, 0.015 mole) was then added and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was poured into chilled saturated $NaHCO_3$ solution (700 mL). The mixture was extracted 3X with methylene chloride (100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum to yield methyl-5-bromo-3-iodobenzoate (5.08 g) as a pink solid. MP = 55-57°C. MS and NMR were consistent with the desired structure.

Step B

To methyl 5-bromo-3-iodobenzoate (Step A above) (5.01 g, 0.015 mole) in anhydrous methylene chloride (100 mL) at -78°C, was added dropwise over two minutes, diisobutylaluminum hydride (5.50 mL, 0.03 mole). The mixture was stirred for 1 hour then allowed to warm to 0°C. The reaction solution was poured into 600 mL, chilled 3N HCl and extracted 3X with methylene chloride (150 mL). The organic layers were combined, dried over

$MgSO_4$ and concentrated under vacuum to yield 5-bromo-3-iod benzyl alcohol (4.54 g) as a white solid. MP = 110-112°C. MS and NMR were consist nt with the desired structure.

Step C

5-Bromo-3-iodobenzyl alcohol (3.01 g, 9.6 mmol) in a 50 mL round bottom flask was stirred magnetically and diluted with 15 mL anhydrous methylene chloride to give a turbid solution. The reaction flask was then stoppered and the septum stopper secured with wire.

Anhydrous methylene chloride (15 mL) was added to a separate 100 mL round bottom flask which was equipped with a cold finger. Nitrogen dioxide (1.72 g, 18.7 mmol) was condensed into the solution of methylene chloride at -20°C.

The benzyl alcohol solution was chilled to 0°C and the nitrogen dioxide/methylene chloride solution was transferred via cannula into the reaction flask under a static nitrogen atmosphere. The reaction solution was stirred magnetically at 0°C for 15 minutes after completion of the nitrogen dioxide solution transfer. The reaction solution was stirred at room temperature for 18 hours.

The reaction flask was vented in the hood and the excess nitrogen dioxide was expelled with a nitrogen stream. The reaction solution was then concentrated by rotary evaporation and resuspended in 30 mL ether. The ether solution was washed with 200 mL 10% sodium bicarbonate in a 500 mL separatory funnel. The resulting aqueous solution was extracted three times with 150 mL ether. The organic layers were combined, dried with sodium sulfate, filtered and concentrated *in vacuo* to afford 2.89 g of a yellow solid.

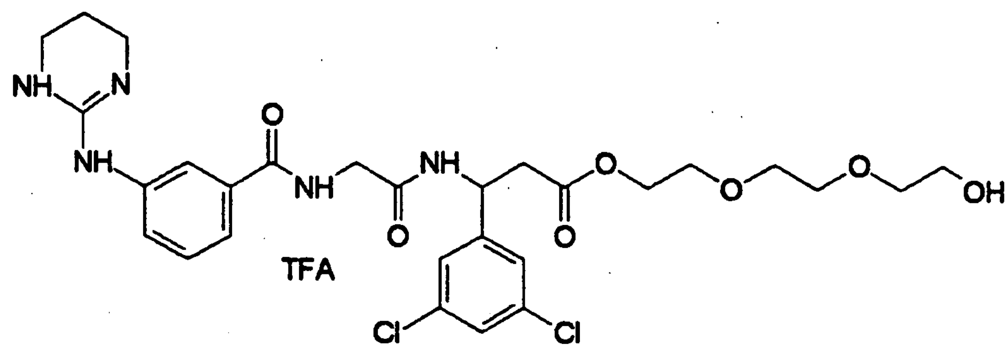
The product was isolated by flash chr matography to yi ld 5-br mo-3-iodobenzaldehyde as a white solid. MS and NMR were consistent with the desired structure.

Step D

The title compound was prepared according to the methodology of Example 175, substituting an equivalent amount of 5-bromo-3-iodobenzaldehyde (Step C, above) for 3,4-dichlorobenzaldehyde in Example 174, Step A. MS and NMR were consistent with the desired structure.

EXAMPLE 220

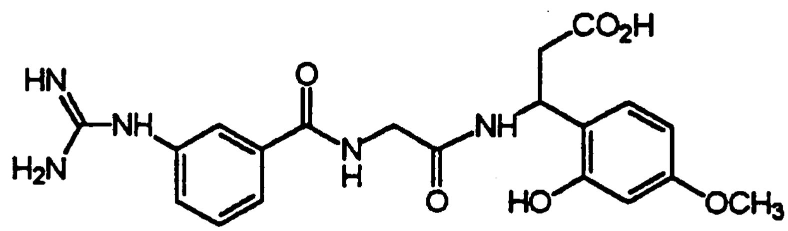
Preparation of (±) [2-[2-(2-hydroxy thoxy)-ethoxy]ethoxy]ethyl] 3,5-dichloro-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]-phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoate, trifluoroacetate salt



The above compound was prepared according to the methodology of Example 217, substituting an equivalent amount of triethyleneglycol for tetraethyleneglycol. MS and NMR were consistent with the desired structure.

Example 222

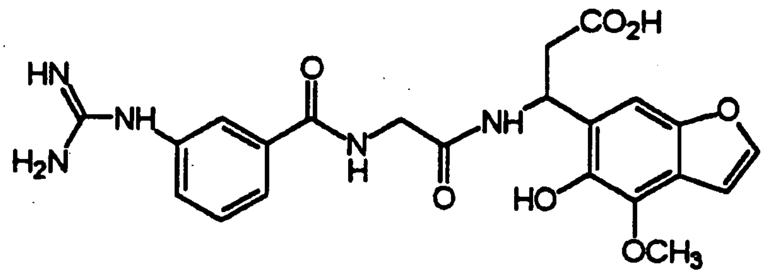
Pr paration of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-2-hydroxy-4-methoxybenzenepropanoic acid



(RS)-4-amino-7-methoxy hydrocoumarin hydrochloride (1.26 g, 5.5 mmole), prepared from 7-methoxycoumarin (Aldrich) according to J. Rico, Tett. Let., 1994, 35, 6599-6602, was coupled to GIHA (1.50 g, 5.5 mmole) using substantially the procedure and proportions of Example 86, Step D. Purification by preparative RPHPLC gave the desired product as a mixture of hydrocoumarin (lactone) and phenoxy-acid TFA salts as a light yellow powder after lyophilization (1.25 gm). Essentially complete conversion to the desired phenol-acid can be obtained by dissolving the purified mixture in water, adjusting the pH to 7-8 with dilute aqueous NaOH until reaction is complete by HPLC, and lyophilizing (0.5 gm). MS and NMR were consistent with the desired phenol-carboxylic acid form of the molecule.

Example 223

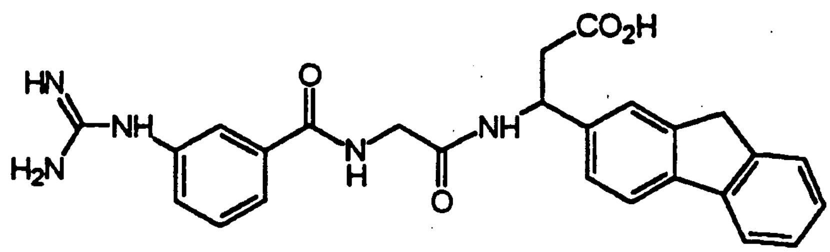
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-hydroxy-4-methoxybenzofuran-6-propanoic acid, trifluoroacetate salt



(RS)-4-amino-8-methoxy-hydropsoralen hydrochloride (2.2 gm, 8.1 mmole), prepared from 8-methoxypsoralen according to J. Rico, Tett. Let., 1994, 35, 6599-6602, was coupled to GIHA (2.0 g, 7.3 mmole) using substantially the procedure and proportions of Example 86, Step D. The product was isolated by preparative RPHPLC as the desired phenol-acid. NMR and MS were consistent with the desired structure.

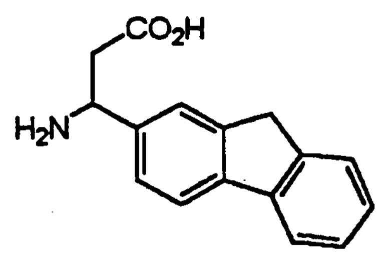
Example 224

Pr paration of (±) β-[[2-[[[3-[(amin imin methyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-9H-fluorene-2-propanoic acid, trifluoroacetate salt



Step A

(±) β-amino-9H-fluorene-2-propanoic acid



2-fluorene-carboxaldehyde (5.0 gm, 26 mmole, Aldrich) was combined with malonic acid (3.25 gm, 31 mmole), ammonium acetate (2.4 gm, 31 mmole), and isopropyl alcohol (70 mL) and refluxed overnight. After cooling the precipitated solid was collected by filtration and dried. NMR and MS were consistent with the proposed structure.

Step B

Ethyl (±) β-amino-9H-fluorene-2-propanoate

The product from Step A was taken up in absolute EtOH, dry HCl gas was added to saturation, and the mixture refluxed overnight. Volatiles were removed and the resulting semi-solid partitioned between ethyl acetate and

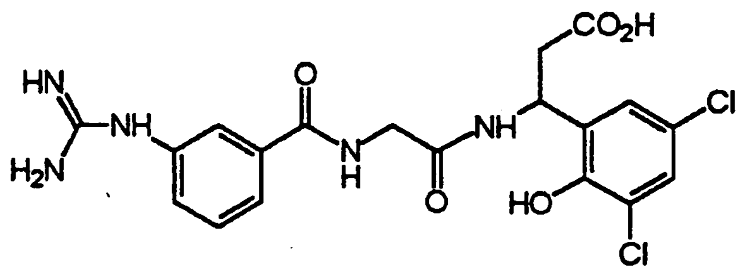
water. The aqueous layer was made basic by addition of 2.5 N NaOH and extracted with EtOAc (2 x 200 mL). Th organic layer was dri d (anhydr us $NaSO_4$) and dry HCl gas added until precipitation ceased. Volatiles were removed until a semisolid residue remained. This was triturated with diethyl ether to obtain a solid that was collected by filtration. NMR and MS were consistent with the proposed structure.

Step C

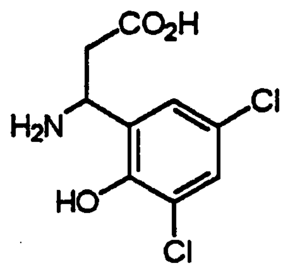
The title compound was prepared in the following manner. GIHA (0.41 gm, 1.5 mmole) was coupled to the product of Step B (0.42 gm, 1.5 mmole) above using substantially the procedure of Example 86, Step D. Preparative RPHPLC was used to isolate the ethyl ester of the title compound. This product (280 mg) was hydrolyzed to the acid by treating an aqueous dioxane solution (1:1) with excess LiOH, acidifying with TFA and purifying the product by RPHPLC. A white amorphous solid is obtained after lyophilization (250 mg). NMR and MS were consistent with the proposed structure.

Example 225

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,5-dichloro-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate



Step A



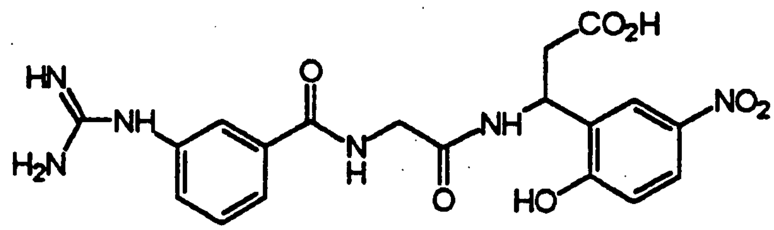
The above compound was prepared by reacting 3,5-dichlorosalicylaldehyde (10.0 gm, 52.4 mmole, Aldrich), malonic acid, and ammonium acetate in isopropyl alcohol using substantially the same procedure and proportions of Example 224, Step A. NMR and MS were consistent with the desired intermediate.

Step B

GHIA (1.0 gm, 3.7 mmole) and the product of Step A (1.1 gm, 4.4 mmole) were coupled using substantially the same procedure and proportions as Example 86, Step D. Desired product was isolated by C-18 RPHPLC and the appropriate fractions combined and lyophilized to give the title compound (0.42 gm). NMR and MS were consistent with the proposed structure.

Example 226

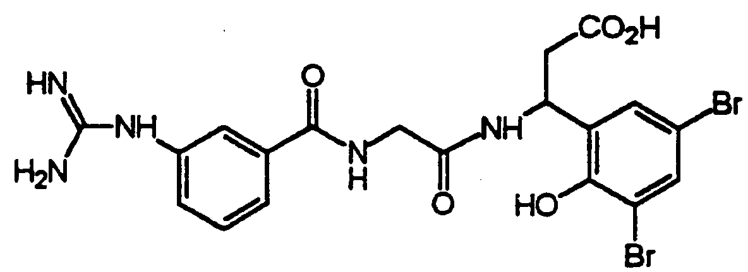
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-2-hydroxy-5-nitrobenzenepropanoic acid, trifluoroacetate salt



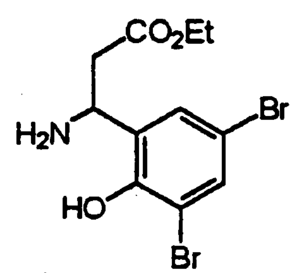
(RS)-4-amino-6-nitro-hydrocoumarin hydrochloride (1.1 g, 4.4 mmole) prepared from 6-nitrocoumarin (Aldrich) according to J. Rico, Tett. Let., 1994, 35, 6599-6602, was coupled to GIHA (1.0 g, 3.7 mmole) using substantially the procedure and proportions of Example 86, Step D. Purification by preparative RPHPLC gave the desired product as a mixture of hydrocoumarin (lactone) and phenoxy-acid TFA salts as a powder after lyophilization. Essentially complete conversion to the desired phenol-acid was obtained by dissolving the purified mixture in water, adjusting the pH to 7-8 with dilute aqueous NaOH until reaction is complete by HPLC, and lyophilizing. MS and NMR were consistent with the desired phenol-carboxylic acid form of the molecule.

Example 227

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dibromo-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate



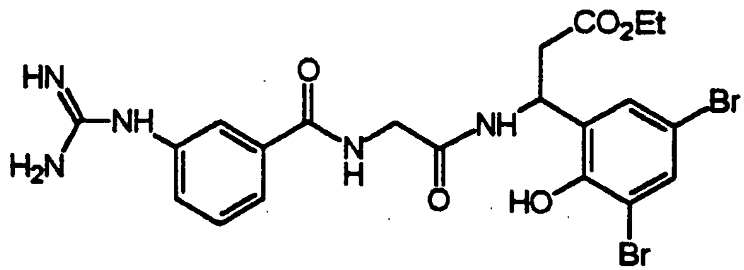
Step A



The above beta amino acid ester hydrochloride salt was prepared according to substantially the methodology of Example 1, Steps A and B substituting 3,5-dibromosalicylaldehyde (20.0 gm, 0.0715 mole, Aldrich) for 3-pyridine carboxaldehyde in Step A and keeping the proportions constant. NMR and MS were consistent with the proposed structure.

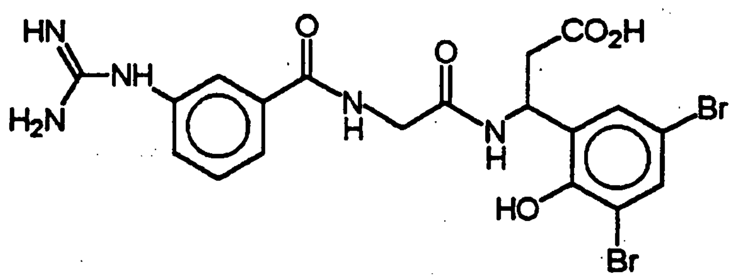
Step B

Ethyl (±) β-[[2-[[[3-[(aminoimin methyl)amino]phenyl]-carb nyl]amino]acetyl]amino]-3,5-dibromo-2-hydroxybenzene-propanoate, trifluoroacetate salt, monohydrate



GHIA (1.0 gm, 3.7 mmole) and the product of Step A (1.78 gm, 4.4 mmole) were coupled using substantially the same procedure and proportions as Example 86, Step D. The desired product was isolated by C-18 RPHPLC and the appropriate fractions combined and lyophilized to give ethyl (±) β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-carbonyl]amino]acetyl]amino]-3,5-dibromo-2-hydroxybenzenepropanoate, trifluoroacetate salt, monohydrate (0.52 gm). NMR and MS were consistent with the proposed structure.

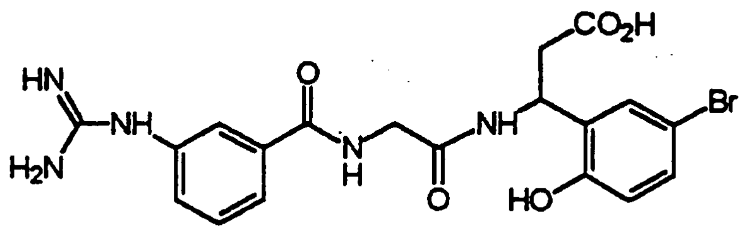
Step C



The product obtained in Step B was converted to the acid using substantially the procedure and conditions of Example 6, however, the hydrolysis solvent was dioxane:water. Preparative C-18 RPHPLC purification gave the TFA salt (300 mg). NMR and MS were consistent with the proposed structure.

Example 228

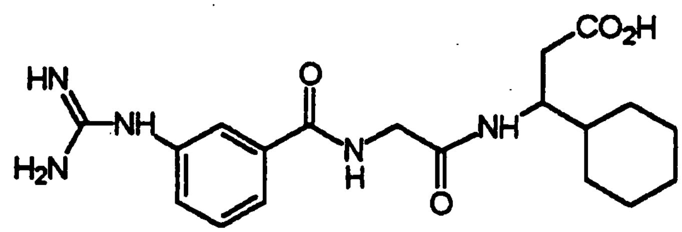
Preparation f (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-5-bromo-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate



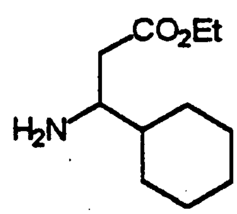
The title compound was prepared using substantially the procedure and proportions of Example 224, and substituting 5-bromosalicylaldehyde for 3,5-dichlorosalicylaldehyde to obtain the ethyl ester of the title compound. After ester hydrolysis the acid-phenol was obtained (0.3 gm after lyophilization). NMR and MS were consistent with the proposed structure.

Example 229

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-cyclohexanepropanoic acid, trifluoroacetate salt, monohydrate



Step A



To a solution of ethyl (R,S)-3-amino-3-phenyl propionate hydrochloride (1.7 gm) dissolved in absolute EtOH (70 mL) was added 5% Pt on carbon and the reaction mixture transferred to a pressure bottle. After purging, the reaction vessel was pressurized with hydrogen (54 psig) and the reaction allowed to go to completion. Volatiles were removed and the product used without further purification. NMR and MS were consistent with the proposed structure.

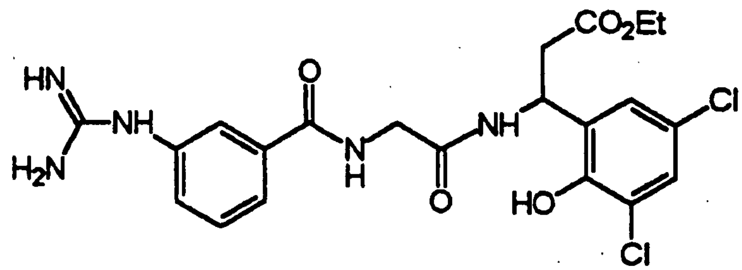
Step B

Ethyl (R,S)3-amino-3-cyclohexylpropionate hydrochloride and GIHA were coupled using substantially the same procedure and proportions as Example 86, Step D.

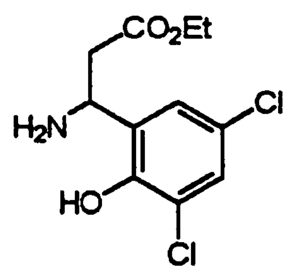
Ethyl (±) β-[[2-[[[3-[(aminoiminomethyl)amino]ph nyl]-carbonyl]amino]acetyl]amino]cycl hexane pr panoic acid, trifluoroacetat salt, monohydrate was isolated using C-18 RPHPLC and lyophilized to give a white amorphous powder. Ethyl (±) β-[[2-[[[3-[(aminoiminomethyl)amino]phenyl]-carbonyl]amino]acetyl]amino]cyclohexane propanoic acid, trifluoroacetate salt, monohydrate was hydrolyzed using the procedure of Example 224, Step C to give the title compound (0.5 gm). NMR and MS were consistent with the proposed structure.

Example 230

Preparation of (±) ethyl β-[[2-[[[3-[(aminoimin methyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3,5-dichloro-2-hydroxybenzenepropanoate, trifluoroacetate salt, monohydrate



Step A



(RS)-4-Amino-6,8-dichlorocoumarin hydrochloride was prepared according to the procedure of Example 233, Steps A and B substituting 3,5-dichloro-salicylaldehyde for 3-bromo-5-chlorsalicylaldehyde in Example 233, Step A.

The above beta amino ethyl ester hydrochloride salt was prepared by dissolving the (RS)-4-amino-6,8-dichlorohydrocoumarin hydrochloride (8.0 g, 0.0207 mole) in absolute EtOH (30 mL) and adding 4 N HCl in dioxane (10 mL) and stirring the reaction mixture at room temperature for 2.5 hours. Excess HCl was removed by rotary evaporation (cold) and the reaction mixture was concentrated to a solid (50°C). The solid was treated with EtOAc (25 mL) and Et_2O (10 mL) and stirred to give a white solid that was isolated by filtration (5.84 g). MS and NMR were consistent with the desired beta-amino acid

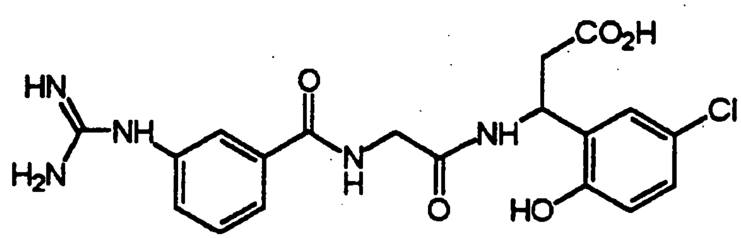
thyl ester as the hydrochloride salt.

Step B

To a solution of GIHA HCl (3.4 gm, 0.0124 mole) dissolved in dimethylacetamide (40 mL) was added N-methylmorpholine NMM, (1.36 mL, 0.0124 mole) and the solution cooled to 0-5°C with gentle stirring. Isobutylchloroformate (1.61 mL, 0.0124 mole) was added and the reaction allowed to proceed for about 10 minutes. At this point a solution of the product of Step A (3.90 gm, 0.0124 mole) and NMM (1.36 mL) in DMA (20 mL) were added to the reaction mixture and the coupling allowed to proceed overnight. Volatiles were removed and the reaction mixture redissolved in acetonitrile:water and brought to pH of about 2 by the addition of TFA. The desired product was isolated by preparative C-18 RPHPLC and lyophilized to obtain the TFA salt (2.61 gm). NMR and MS were consistent with the structure of the title compound.

Example 231

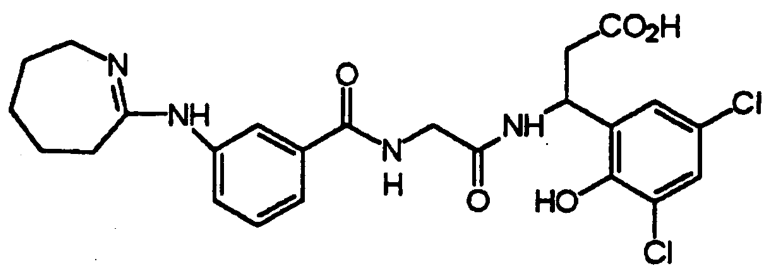
Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-5-chloro-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate



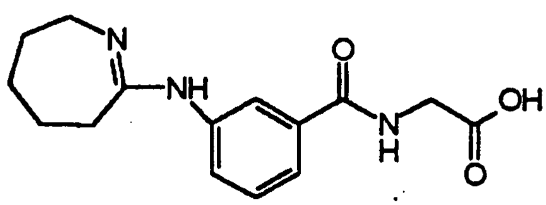
The above compound was prepared using substantially the procedure and proportions of Example 224 and substituting 5-chlorosalicylaldehyde for 3,5-dichlorosalicylaldehyde. After final ester hydrolysis the acid-phenol was obtained (0.3 gm after lyophilization). NMR and MS were consistent with the proposed structure.

Example 232

Preparati n of (±) 3,5-dichloro-2-hydroxy-β-[[2-[[[3-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt, monohydrate



Step A



To m-aminohippuric acid (2.0 gm, 8.7 mmole) in acetonitrile (50 mL) was added 1-aza-2-methoxy-1-cycloheptane (1.2 gm, 9.5 mmole) (Aldrich). The reaction was allowed to proceed at room temperature over a weekend. Solvent was removed and the residue triturated with diethyl ether to give a solid (1.6 gm) that was substantially pure 3-(1-aza-2-amino-1-cycloheptane)-hippuric acid by analytical RPHPLC, MS and NMR.

Step B

The product obtained in Step A, 3-(1-aza-2-amino-1-cycloheptan)-hippuric acid (1.0 gm, 3.2 mmole) was

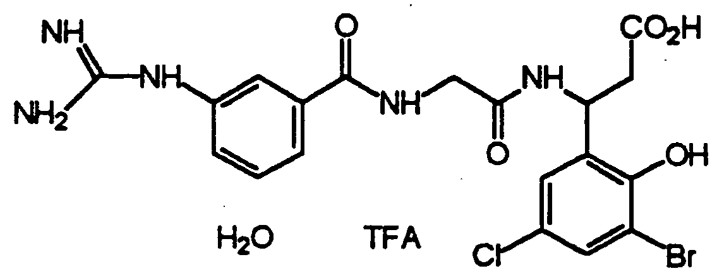
coupled to the compound prepared in Example 230, Step A (1.0 gm, 3.2 mmol), using substantially the conditions and procedure of Example 230, Step B and substituting 3-(1-aza-2-amino-1-cycloheptane)-hippuric acid for GIHA. Purification by C-18 RPHPLC gave the ethyl ester of the title compound (0.5 gm). NMR and MS were consistent with the proposed structure.

Step C

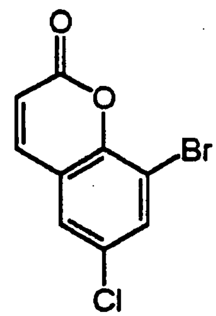
The product prepared in Step B (0.35 gm), was dissolved in dioxane-water (1:1, 30 mL) and the pH adjusted to about 11 by addition of LiOH (NaOH may be freely substituted for LiOH). Upon complete hydrolysis to the acid (determined by analytical RPHPLC) the reaction mixture was acidified to about pH 2-3 by addition of TFA and the desired compound was isolated by preparative scale C-18 RPHPLC. NMR and MS were consistent with the structure of the title compound.

Example 233

Pr paration of (±) β-[[2-[[[3-[(amin iminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-bromo-5-chloro-2-hydroxybezenepropanoic acid, trifluoroacetate salt, monohydrate

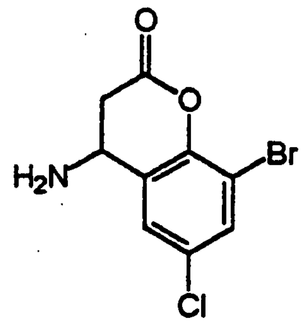


Step A



A solution of 3-bromo-5-chlorosalicylaldehyde (11.0 gm, 0.047 mole and triethylamine (5.6 mL) dissolved in acetic anhydride (14.0 mL) was heated to reflux for 4 hours. The reaction was allowed to cool to room temperature and volatiles were removed under vacuum. The resulting solid was partitioned between EtOAc and aqueous sodium bicarbonate and the layers separated. The aqueous layer was re-extracted with EtOAc and the organic layers combined, dried (Na_2SO_4) and volatiles removed under vacuum to obtain a solid (13.5 gm). NMR and MS were consistent with the proposed structure.

Step B



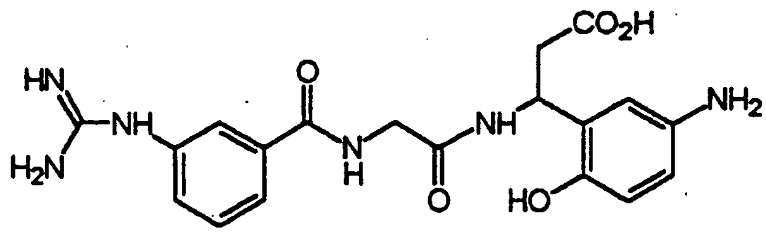
The product obtained in Step A (10.0 gm, 0.039 mole) was converted to (RS)-4-amino-6-chloro-8-bromo-hydrocoumarin hydrochloride (5.1 g, 18.5 mmole) according to J. Rico, Tett. Let., 1994, 35, 6599-6602 with the following modification: the addition product obtained by the addition of lithium bis-trimethylsilylamide to the coumarin of Step A was quenched by addition of one equivalent HOAc at 0°C prior to workup.

Step C

The product of Step B (4.0 gm, 0.013 mole) was coupled to GHIA HCl (3.3 gm, 0.012 mole) using substantially the procedure of Example 230 but substituting the compound obtained in Step B for the compound of Example 30, Step A to give, after C-18 RPHPLC purification and hydrolysis of the appropriate fraction according to the procedure of Example 232, Step C, the desired compound (TFA salt) as a fluffy, white powder (4.8 g) after lyophilization. NMR and MS were consistent with the proposed structure.

Example 234

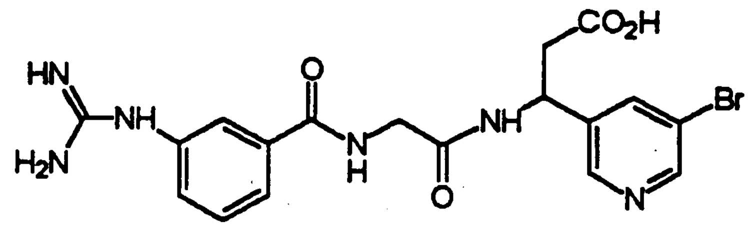
Preparation of (±) 5-amino-β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-2-hydroxybenzenepropanoic acid, bis(trifluoroacetate) salt, monohydrate



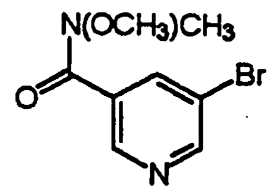
The product from Example 226 (0.5 gm) was dissolved in AcOH:H_2O (2:1, 60 mL) and 3% Pd on carbon added (0.5 gm, Aldrich). The reaction mixture was pressurized with hydrogen (20 psig) and allowed to react with vigorous stirring for 2 hours. Catalyst was removed by filtration and the mixture concentrated to a thick oil. The oil was dissolved in water and the desired compound isolated by C-18 RPHPLC. NMR and MS were consistent with the proposed structure.

Example 235

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-5-bromopyridine-3-propanoic acid, bis(trifluoroacetate) salt, monohydrate

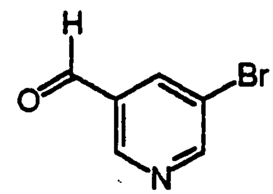


Step A



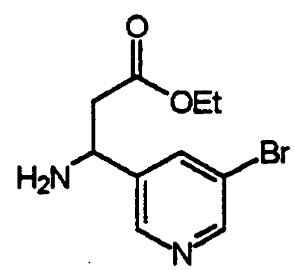
To a solution of 5-bromonicotinic acid (20.0 gm, 0.10 mole), O,N-dimethylhydroxylamine (9.8 gm, 0.1 mole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt in DMF (200 mL) was added 1-hydroxytriazole (200 mL of 0.5 M solution in DMF, 0.10 mole) and triethylamine (19.7 mL, 0.14 mole) and the reaction mixture stirred vigorously for 18 hours. Volatiles were removed under vacuum at 60°C until a mush remained. The reaction mixture was partitioned between ethyl acetate (300 mL) and saturated aqueous sodium bicarbonate, the layers separated and the aqueous layer re-extracted with EtOAc. The organic layers were combined dried (Na_2SO_4) and concentrated to a dark yellow oil (21.4 gm). NMR and MS were consistent with the proposed structure.

Step B



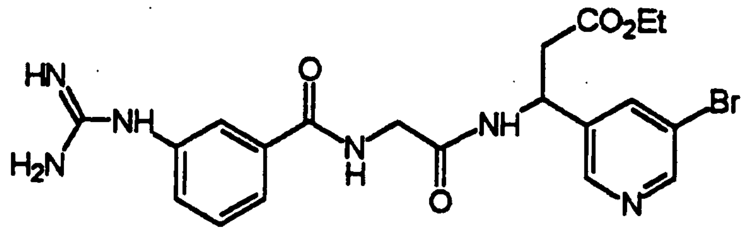
A solution of the product of Step A (12.9 gm, 0.053 mole) in THF (300 mL) was cooled to 0°C and LAH in THF (53 mL of 1.0 M stock solution, Aldrich) was added via syringe. After 0.5 hour $KHSO_4$ (19.6 gm, 0.13 mole, in 100 mL water) was added. After several minutes dilute aqueous HCl (50 mL) was added and the organic layer separated, dried (Na_2SO_4) and volatiles removed to obtain a yellow oil that solidifies on standing. The solid was purified by sublimation to give the title compound as a white solid (7.8 gm). NMR and MS were consistent with the proposed structure.

Step C



The above beta amino acid ester hydrochloride salt was prepared according to substantially the methodology of Example 1, Steps A and B substituting the compound of Step B (6.24 gm, 0.034 mole) for 3-pyridine carboxaldehyde in Step A and keeping the proportions constant. The product was isolated as the di-TFA salt by C-18 RPHPLC. NMR and MS were consistent with the proposed structure.

Step D



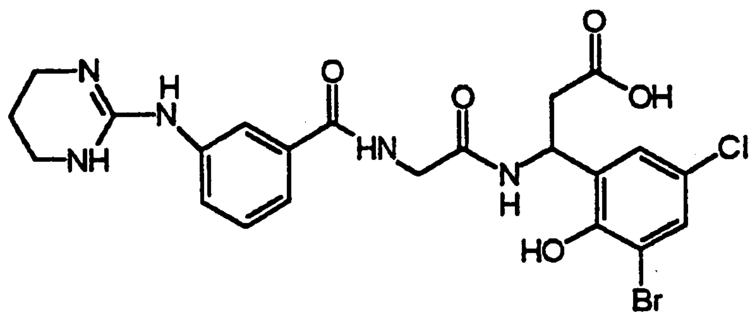
The product of Step C was coupled to GIHA HCl (0.5 gm, 1.8 mmole) using substantially the procedure of Example 230, Step B and substituting the product of Step C above (and correspondingly two equivalents of NMM) for the product of Example 230, Step A. The ethyl ester of the product was isolated as the di-TFA salt by C-18 RPHPLC. NMR and MS were consistent with the proposed structure.

Step E

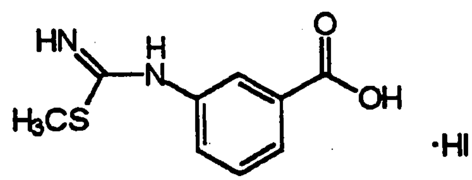
Hydrolysis of the product of Step D (200 mg) to the corresponding acid was accomplished using substantially the procedure of Example 232, Step C. The product was isolated as the di-TFA salt by C-18 RPHPLC and lyophilized to give the title compound as a white solid (150 mg). NMR and MS were consistent with the proposed structure.

Example 236

Preparation of (±) 3-bromo-5-chloro-2-hydroxy-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt, monohydrate

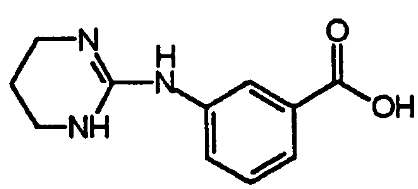


Step A



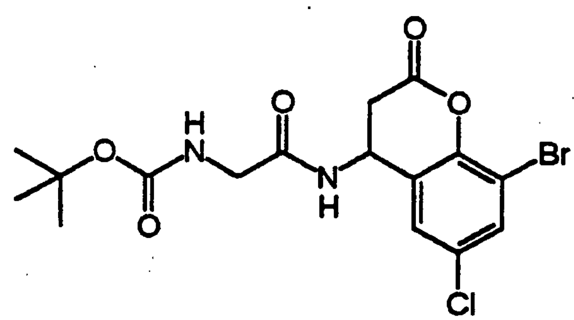
To a solution of 1-(3-carboxyphenyl)-2-thiourea (14.0 gm, 71.3 mmole) in EtOH (absolute, 140 mL) was added iodomethane (10.2 gm) and the solution refluxed for 2.5 hours. Volatiles were removed under vacuum at 60°C to obtain a yellow oil. This was treated with t-butylmethylether and volatiles removed to give a yellow foam that became firm upon cooling. NMR and MS were consistent with the proposed structure.

Step B



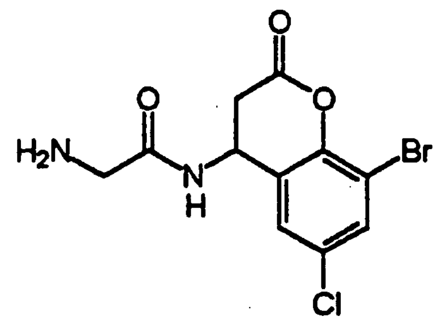
To the product from Step A (5.0 gm, 0.015 mole) dissolved in DMA (50 mL) was added a catalytic amount of DMAP and 1,3-diaminopropane (1.2 gm, 0.016 mole) and the solution heated to 100°C for 48 hours. Volatiles were removed until a thick oil remained. This was treated sequentially with EtOAc, Et_2O and MeOH (50 mL) to obtain a solid that was isolated by filtration. This product was suspended in 4 N HCl in dioxane and stirred for several hours. The resulting solid was filtered, washed with Et_2O and dried (800 mg). NMR and MS were consistent with the proposed structure as the HCl salt.

Step C



To a solution of (RS)-4-amino-6-chloro-8-bromo-hydrocoumarin hydrochloride (2.6 g) prepared in Example 233, Step B, dissolved in THF (50 mL) was added triethylamine (1.0 mL) and N-t-Boc-glycine-N-hydroxysuccinimide ester (2.0 gm, Sigma) and the reaction allowed to proceed to completion. Volatiles were removed and the residue partitioned between EtOAc and water. The organic layer was separated, washed with dilute aqueous HCl, saturated sodium bicarbonate and dried (Na_2SO_4) and concentrated to a dark foam (3.2 gm). This product was used in the next step without further purification.

Step D



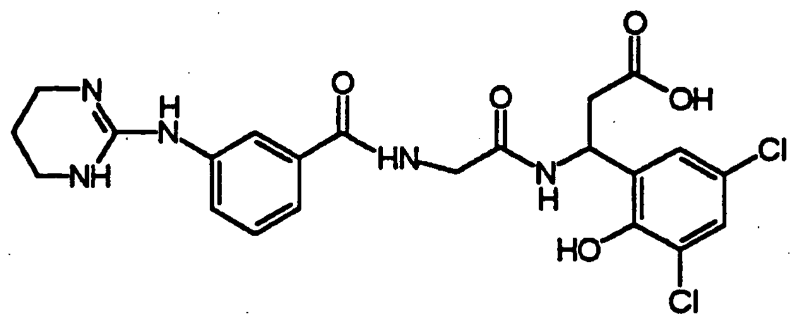
The BOC protecting group was removed by dissolving the reaction mixture obtained in Step C in dioxane (20 mL) and to the well stirred solution HCl (4 N in dioxane, Aldrich) was added. Upon cessation of gas evolution (about 0.5 hour) volatiles were removed to obtain a dark residue that was triturated with diethylether to obtain, upon filtration, a yellow solid (2.46 gm). NMR and MS were consistent with the proposed structure as the hydrochloride salt.

Step E

The product from Step D (1.4 gm) and the product from Step B (1.0 gm) were coupled using substantially the procedure of Example 230, Step B. Upon completion of the coupling reaction volatiles were removed from the crude reaction mixture. The reaction mixture was subsequently redissolved in dioxane:water and the pH adjusted to approximately 11 by addition of aqueous NaOH. The pH was maintained above 10 until complete hydrolysis was observed by analytical RPHPLC. At this point the pH was adjusted to 2-3 by addition of TFA and the desired product isolated by preparative C-13 RPHPLC (0.35 gm after lyophilization). NMR and MS were consistent with the proposed structure as the TFA salt.

Example 237

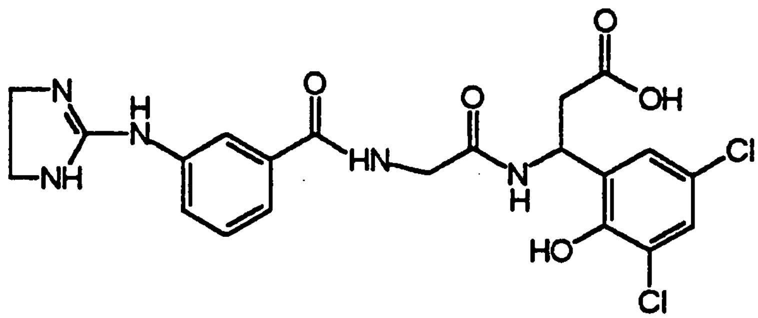
Preparation of (±) 3,5-dichloro-2-hydr xy-β-[[2-[[[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)-amino]phenyl]carbonyl]amino]acetyl]amino]-benzenepropanoic acid, trifluoroacetate salt, monohydrate



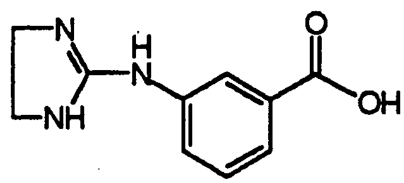
The above compound (350 mg) was prepared using essentially the conditions and procedures of Example 236 but substituting (RS)-4-amino-6,8-dichloro-hydrocoumarin hydrochloride prepared from the corresponding salicylaldehyde according to the procedure in Example 233, Steps A and B, for (RS)-4-amino-6-bromo-8-chlorohydrocoumarin hydrochloride in Step E. NMR and MS were consistent with the proposed structure as the TFA salt.

Example 238

Preparation f (±) 3,5-dichloro-β-[[2-[[[3-[(4,5-dihydro-1H-pyrrolidin-2-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate

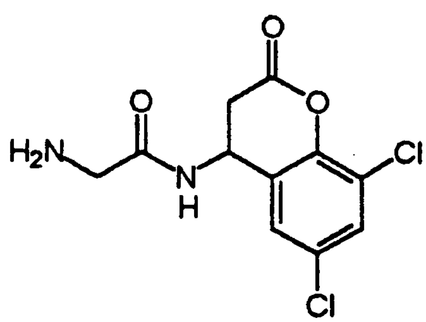


Step A



The above compound was prepared according to the procedure of Example 236, Steps A and B by substituting ethylene diamine (1,2-diaminoethane) for 1,3-diaminopropane in Step B.

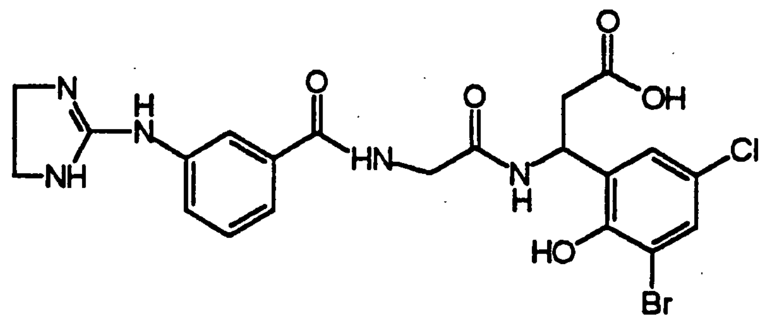
Step B



The desired end pr duct (300 mg) was prepared by coupling the product of Step A with the hydrochl ride salt of the above compound (prepared in Exampl 237) according to the coupling procedure of Example 237. NMR and MS were consistent with the proposed structure as the TFA salt.

Example 239

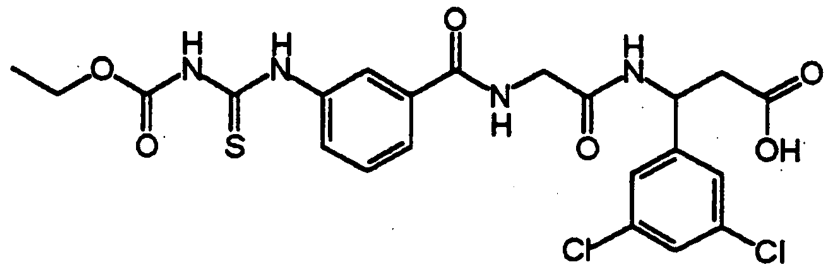
Preparation of (±) 3-bromo-5-chloro-β-[[2-[[[3-[(4,5-dihydro-1H-pyrrolidin-2-yl)amino]phenyl]carbonyl]-amino]acetyl]amino]-2-hydroxybenzenepropanoic acid, trifluoroacetate salt, monohydrate



The above compound was prepared according to the procedure of Example 238 by substituting the product of Example 238, Step A for the product of Example 237, Step B. NMR and MS were consistent with the proposed structure as the TFA salt.

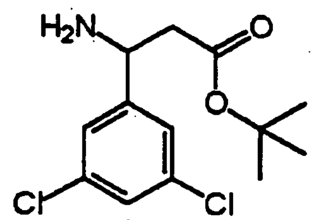
Example 240

Preparation of 3,5-dichloro-β-[[2-[[[3-[[[(ethoxycarbonyl)amino]thioxomethyl]amino]phenyl]carbonyl]amino]acetyl]amino]benzenepropanoic acid



Step A

3-Amino-3-(3,5-dichlorophenyl)propionic acid, tert-butyl ester

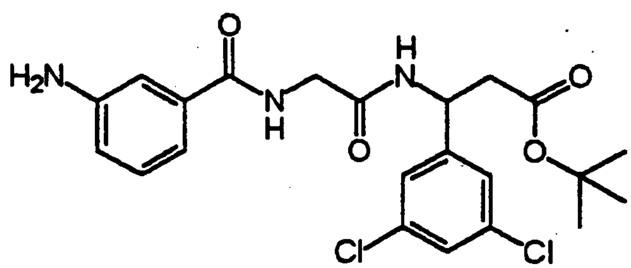


1

A mixture of 13.5 g of 1-bromo-3,5-dichlorobenzene (Aldrich, 13.5 g), tert-butyl acrylate (Aldrich, 11.1 mL), triethylamine (8.4 mL), $Pd(OAc)_2$ (0.12 g), tris-p-tolylphosphine (0.9 g) and acetonitrile (20 mL) was prepared in a steel bomb under nitrogen. The vessel was sealed and heated to 120°C for 16 hours. Chloroform (40 mL) was added to the cooled reaction mixture and the mixture was extracted with ether and water. The organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was rapidly filtered through silica gel using 8% ethyl acetate in hexane as

eluant, to provid 13 g of a thick liquid. A mixture of this product (12.6 g) tert-butanol (35 mL) and ammonia (40 mL) in a st el bomb was heated to 80°C for 25 hours (pressure, at room temperature was 130 psi; at 80°C, 500 psi). After cooling and venting, the contents were concentrated *in vacuo*. The residue was extracted with ethyl acetate (100 mL) and cold, dilute hydrochloric acid (1N, 100 mL) added. The aqueous phase was basified with solid K_2CO_3 and extracted with ether and methylene chloride. The organic phase was dried over K_2CO_3 and concentrated *in vacuo* to give the above compound (11 g) as a thick, reddish brown liquid.

Step B



To a stirred solution of 3-nitrobenzoyl chloride (7 g, Aldrich) in CH_2Cl_2 at -78°C was added glycine methyl ester hydrochloride (5 g, Aldrich) followed by triethylamine (20 mL). The mixture was allowed to warm to room temperature over 16 hours. The volatiles were removed and the residue was extracted with ethyl acetate and water. The organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was stirred in tetrahydrofuran (50 mL) and aqueous lithium hydroxide (50 mL, 1M) for 15 minutes. The volatiles were removed and the residue was treated with hydrochloric acid (50 mL, 3M) and extracted with ethyl acetate and water. The organic phase was washed with water, dried ver $MgSO_4$

and concentrated *in vacuo*. To a stirred solution of the residue (2.24 g) in tetrahydrofuran (15 mL) at -78°C was added in succession 4-methylmorpholin (1.1 mL, Aldrich) and isobutyl chloroformate (1.3 mL, Aldrich). After 30 minutes, 3-amino-3-(3,5-dichlorophenyl)propionic acid, tert-butyl ester (2.91 g, prepared in Step A) was added. The mixture was allowed to warm to room temperature over 2 hours. The volatiles were removed and the residue was extracted with ethyl acetate and water. The organic phase was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the residue in tetrahydrofuran and ethanol (1:1, 30 mL) was shaken in a Parr hydrogenator with 3% Pd/C (0.5 g) under 5 psi hydrogen pressure for 5 hours. The mixture was filtered and the filtrate concentrated to provide the above compound as a thick gum. This sample was used without further purification.

Step C

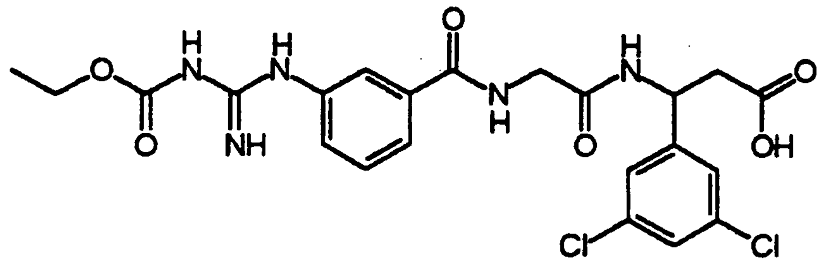
A mixture of the compound of Step B (1.2 g) and ethoxycarbonyl isothiocyanate (Aldrich, 0.3 μL) in toluene (5 mL) was heated to reflux for 30 minutes. The mixture was concentrated and the residue chromatographed over silica gel to give the t-butyl ester of the title compound (0.78 g) as a white solid. A solution of the t-butyl ester (0.3 g) in trifluoroacetic acid (4 mL) was allowed to stand at 23°C for 16 hours. The volatiles were removed and the residue purified by HPLC to give the title compound as a white solid.

$C_{22}H_{22}N_4O_6S$. 0.5 H_2O

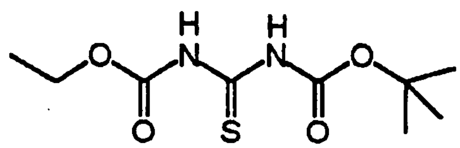
Calculated:	C, 48.01; H, 4.21; N, 10.18; S, 5.83
Found:	C, 47.61; H, 4.11; N, 9.94; S, 5.83

EXAMPLE 241

Preparation of 3,5-dichloro-β-[[2-[[[3-[[[(ethoxycarbonyl)amino]iminomethyl]amino]-phenyl]carbonyl]amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt, monohydrate

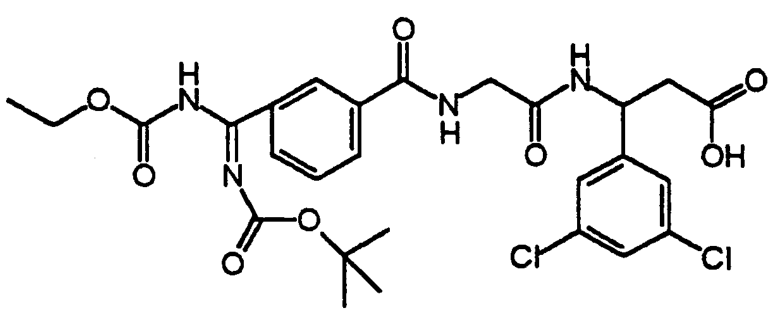


Step A



A mixture of tert-butyl carbamate (Lancaster, 5 g) and ethoxycarbonyl isothiocyanate (Aldrich, 5 mL) in toluene (15 mL) was heated to reflux for 2 hours. The solution was allowed to cool to room temperature over 16 hours. The precipitated solid was filtered and washed with hexane to give the above compound (5.5 g) as a white solid.

Step B



To a stirred solution of the comp und produced in Example 240, St p B (1.3 g) and the product of Step A (0.7 g) in DMF (7 ml) at -15°C was added, in succession, mercuric chloride (0.77 g) and triethylamine (0.8 mL). The mixture was allowed to warm to room temperature over 1 hour and continued stirring for 1 hour more. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography to give the above compound as a white solid.

Step C

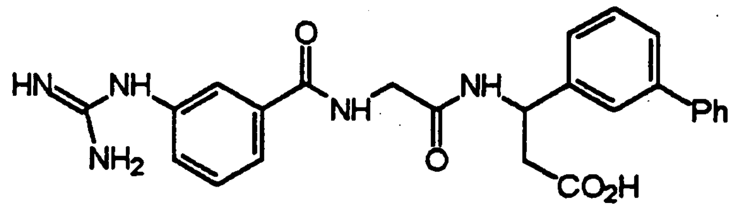
A solution of the product of Step B (0.5 g) in trifluoroacetic acid (10 mL) was allowed to stand at 23°C for 2 hours. The volatiles were removed and the residue purified by HPLC to give the title compound as a white solid.

$C_{22}H_{23}N_5O_6Cl_2$. 1.25 CF_3COOH. 0.5 H_2O

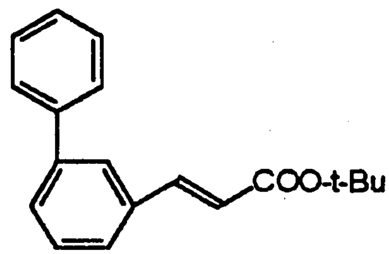
Calculated:	C, 42.96; H, 3.86; N, 10.23; Cl, 10.35
Found:	C, 43.21; H, 3.49; N, 10.20; Cl, 10.52

Example 242

Preparation of β-[[2-[[[3-[(amin iminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino][1,1'-biphenyl]-3-propanoic acid



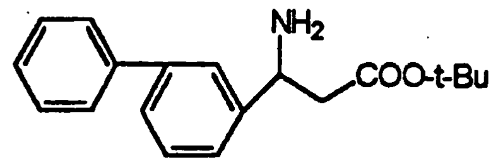
Step A



A mixture of 9.64 g (41.4 mmoles) of 3-bromobiphenyl, 5.8 ml (4.2 g, 41 mmoles) of triethylamine, 6.73 g (52.6 mmoles) of t-butyl acrylate, 624 mg (2.05 mmoles) of tri-p-tolylphosphine, and 83 mg of palladium acetate in 15 ml of dimethylformamide was stirred overnight at 110° in an oil bath. After cooling, the mixture was partitioned between ethyl acetate and water and the aqueous layer further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. Chromatography of the residue over silica gel using mixtures of dichloromethane and hexane as eluents gave the above compound, 10.5 g , as a very pale yellow oil.

^{1}H NMR ($CDCl_3$) 7.77-7.36 (m, 9H), 7.69 (d, J=15Hz, 1H), 6.47 (d, J=15Hz, 1H), 1.58 (s, 9H).

Step B

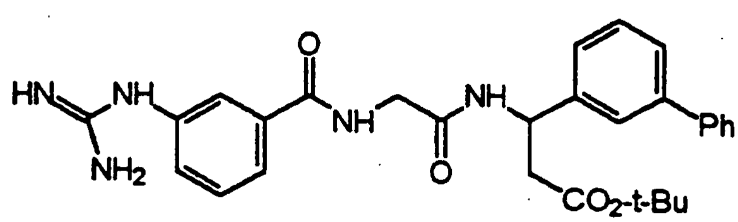


A mixture of 10.5 g (37.5 mmoles) of the product of Step A, 50 ml of liquid ammonia, 5.2g of acetic acid, and 80 ml of t-butanol was heated at 100°C for 18 hours. After cooling, the mixture was concentrated and partitioned between ethyl acetate and aqueous sodium bicarbonate. The aqueous layer was further extracted with ethyl acetate, the combined organic extracts washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using ethyl acetate and then 10% methanol - 1% ammonium hydroxide - 89% ethyl acetate as eluents gave the above compound, 4.75 g, as a colorless oil.

Analysis Calcd. for $C_{19}H_{23}NO_2$ 1/8H_2O (MW 299.65):
C, 76.16; H, 7.74; N, 4.67.
Found: C, 76.29; H, 7.57; N, 4.66.

Step C

1,1-dimethylethyl β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino][1,1'-biphenyl]-3-propanoate



To a solution of 1.00 g (3.66 mmol) f the c mpound of Example M in 20 ml f dry dimethylf rmamide stirred in an ice bath under an arg n atmosphere was added 467 µl (3.84 mmol) of N-methylpiperidine, producing a white solid. After stirring for 15 minutes, 500 µl (3.84 mmoles) of isobutyl chloroformate was added dropwise and stirred continuously for about 20 minutes, resulting in a homogeneous solution. A solution of 1.09 g (3.66 mmoles) of the product of Step B in 5 ml of dimethylformamide was added and the mixture stirred overnight at room temperature. The mixture was concentrated to give 2.88g of an orange oil. Reverse phase preparative HPLC of 1.50 g of the crude mixture using a gradient of 90% to 50% aqueous trifluoroacetic acid - acetonitrile followed by evaporation of appropriate fractions gave the above compound, 800 mg, as a white solid.

^{1}H NMR ($CDCl_3$-DMSO) 8.93 (br s, 1H), 8.56 (t, 1H), 8.22 (d, 1H), 7.81-7.12 (m, 13H, 5.46 (dd, 1H), 4.12 (t, 2H), 2.88 (dd, 1H), 2.77 (dd, 1H), 1.31 (s, 9H).

Step D

A solution of 800 mg of the product of Step C in 10 ml of dichloromethane was added 10 ml of trifluoroacetic acid, and the mixture stirred overnight at room temperature. After concentration, reverse phase preparative HPLC using mixtures of aqueous trifluoroacetic acid - acetonitrile as eluent gave, after evaporation of appropriate fractions, the above compound (250 mg) as a pure white solid.

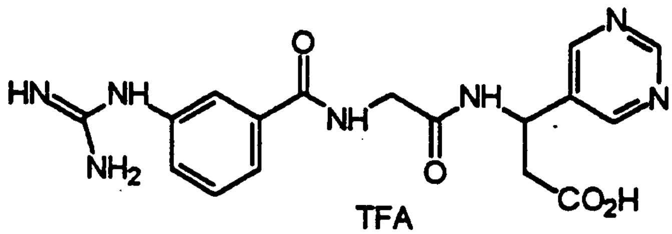
Analysis for $C_{25}H_{26}N_5O_4$ CFCOOH $1/2H_2O$ (MW 581.53):

Calc'd.: C, 55.77; H, 4.33; N, 12.04.

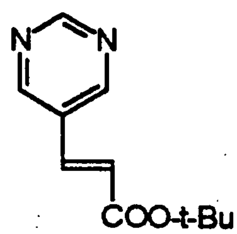
Found: C, 55.81; H, 4.57; N, 11.68.

Example 243

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino][pyrimidine-5-propanoic acid, trifluoroacetate salt



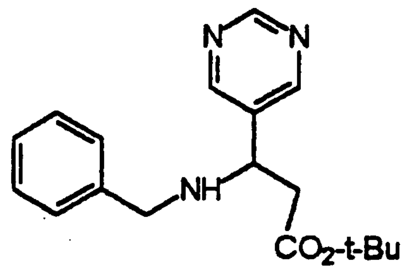
Step A



A mixture of 5.00 g (31.1 mmoles) of 5-bromopyrimidine, 3.14 g (31.1 mmoles) of triethylamine, 5.06 g (39.5 mmoles) of t-butyl acrylate, 475 mg of tri-o-tolylphosphine, and 63 mg of palladium acetate in 11 ml of acetonitrile was stirred at reflux under argon for 8 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, the combined organic extracts washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using a gradient of 30-50% ethyl acetate - hexane gave the above compound, 0.99 g, as a white crystalline solid.

^{1}H NMR ($CDCl_3$) 9.19 (s, 1H), 8.86 (s, 2H), 7.53 (d, J=15Hz, 1H), 6.54 (d, J=15Hz, 1H), 1.55 (s, 9H).

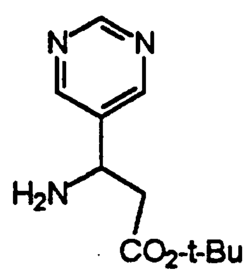
Step B



A solution of 1.28 g (6.21 mmoles) of the product of Step A in 12 ml of benzylamine was stirred in a 70-80° oil bath overnight. After cooling, the excess benzylamine was evaporated. Chromatography of the residue over silica gel using 50% ethyl acetate - hexane as eluent gave the above compound, 1.33 g, as a colorless oil.

^{1}H NMR ($CDCl_3$) 9.18 (s, 1H), 8.78 (s, 2H), 7.21 (m, 5H), 4.14 (t, 1H), 3.68 (d, 1H), 3.59 (d, 1H), 2.73 (dd, 1H), 2.57 (dd, 1H), 1.41 (s, 9H).

Step C

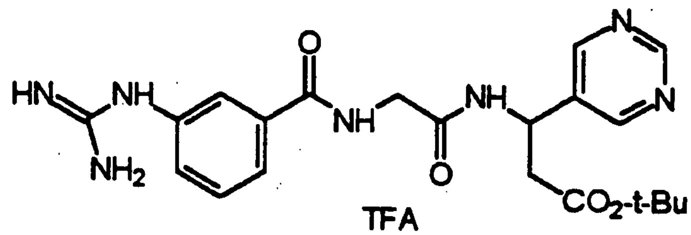


To a solution of 1.33 g (4.25 mmoles) of the product of Step B in 50 ml of 4:1 ethanol - cyclohexene was added 10% palladium on carbon. The mixture was stirred at reflux overnight under argon, 35 mg of pyridinium p-toluenesulfonate was added, and refluxing continued for another 8 hours. After cooling, the mixture was filtered through a filtering aid, and the filtrate concentrated. The residue was filtered through silica gel using 10%

methan 1 - ethyl acetate as elu nt to give th abov comp und (852 mg) as a waxy solid.

^{1}H NMR ($CDCl_3$) 9.26 (s, 1H), 8.78 (s, 2H) , 4.46 (dd, 1H), 2.64 (m, 2H), 1.81 (br s, 1H), 1.43 (s, 9H).

Step D



To a solution of 1.04 g (3.82 mmoles) of m-guanidinohippuric acid in 8 ml of dry dimethylformamide stirring in an ice bath under argon was added dropwise 398 mg (4.01 mmoles) of N-methylpiperidine, producing a white solid. The mixture was stirred for 10 minutes, and then 1.03 g (4.01 mmoles) of disuccinimidyl carbonate was added as a solid. After stirring for 1.5 hours, a clear, homogeneous solution was obtained, to which was added a solution of 852 mg (3.82 mmoles) of the product of Step C. After stirring overnight at room temperature, the mixture was evaporated to dryness. Reverse phase HPLC of the mixture using mixtures of aqueous trifluoroacetic acid - acetonitrile followed by evaporation of the appropriate fractions gave the above compound (230 mg) as a white solid.

^{1}H NMR ($CDCl_3$ - DMSO) 10.58 (s, 1H), 9.09 (s, 1H), 8.76 (s, 2H), 8.57 (t, 1H), 8.49 (d, 1H), 7.79-7.11 (m, 4H), 5.36 (dd, 1H), 4.07 (t, 2H), 2.90 (dd, 1H), 2.79 (dd, 1H), 1.35 (s, 9H).

Step E

230 mg of the product of Step D was dissolved in 20 ml of 1:1 dichloromethane - trifluoroacetic acid, and the resulting mixture was stirred overnight at room temperature. After evaporation, reverse phase HPLC of the mixture using mixtures of aqueous trifluoroacetic acid - acetonitrile followed by evaporation of the appropriate fractions gave the above compound (183 mg) as a white solid.

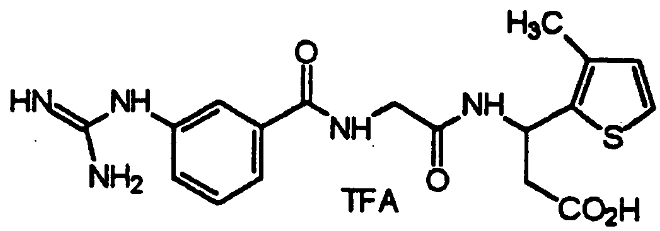
Analysis for $C_{17}N_{19}N_7O_4$ CFCOOH 1/2H_2O (MW 508.41):

Calc'd.: C, 44.89; H, 3.97.

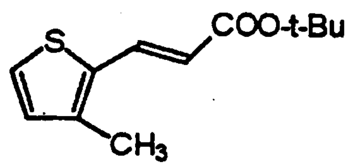
Found: C, 44.75; H, 4.16.

Example 244

Preparati n of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-methylthiophene-2-propanoic acid, trifluoroacetate salt



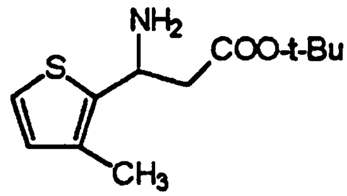
Step A



A mixture of 10.0 g (56.5 mmoles) of 2-bromo-3-methylthiophene, 10.5 ml (9.18 g, 71.8 mmoles) of t-butyl acrylate, 15.7 ml (11.4 g, 113 mmoles) of triethylamine, 857 mg of tri-o-tolylphosphine, and 113 mg of palladium acetate in 20 ml of acetonitrile was stirred at reflux under argon for 8 hours. After cooling, the mixture was partitioned between ethyl acetate and water, the aqueous layer was further extracted with ethyl acetate, the combined organic extracts dried over sodium sulfate, filtered, and evaporated to give the above compound (12.7 g) as a dark red oil.

^1H NMR ($CDCl_3$) 7.78 (d, J=15Hz, 1H), 7.24 (d, J=6Hz, 1H), 6.87 (d, J=6Hz, 1H), 6.13 (d, J=15Hz, 1H), 2.36 (s, 3H), 1.56 (s, 9H).

Step B

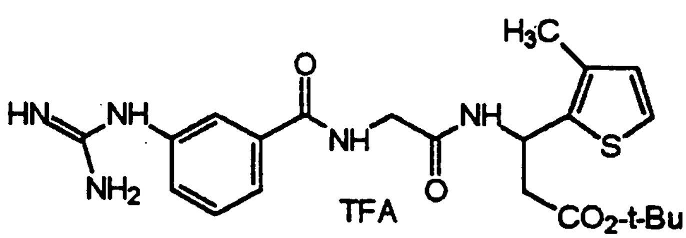


8.00 g (35.7 mmoles) of the product of Step A was reacted with ammonia by the method of Example 242, Step B. Chromatography of the crude product over silica gel using 50% ethyl acetate - hexane as eluent gave the above compound (1.78 g) as a reddish oil that crystallized on standing.

^{1}H NMR ($CDCl_3$) 7.11 (d, 1H), 6.78 (d, 1H), 4.72 (m, 1H), 2.58 (m, 2H), 2.23 (br s, 2H), 2.21 (s, 3H), 1.44 (s, 9H).

Step C

1,1-dimethylethyl β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-methylthiophene-2-propanoate



To a solution of 1.13 g (4.15 mmoles) of m-guanidinohippuric acid in 20 ml of dry dimethylformamide stirring in an ice bath under argon was added dropwise 530 μl (432 mg, 4.36 mmoles) of N-methylpiperidine, producing a white solid. To this mixture was added 1.12 g (4.36

mmoles) of disuccinimidyl carbonat as a solid, and the r sulting mixture stirred for 30 minutes, producing a clear solution. A solution of 1.00 g (4.15 mmol s) of the product of Step B in 8 ml of dimethylformamide was added, the mixture stirred overnight at room temperature. Evaporation of the volatiles gave 3.8 g of residue. Reverse phase HPLC of 1.5 g of the mixture using mixtures of aqueous trifluoroacetic acid - acetonitrile followed by evaporation of the appropriate fractions gave the above compound (171 mg) as an off white solid which was identified by conversion to the acid as described in Step D.

Step D

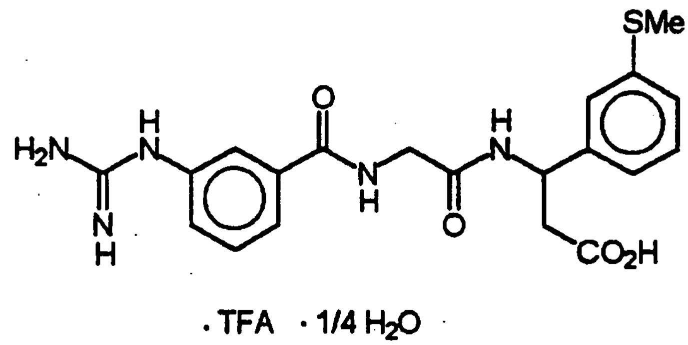
A solution of 167 mg of the product of Step C in 15 ml of 1:1 dichloromethane - trifluoroacetic acid was stirred overnight at room temperature. Reverse phase HPLC of the residue using mixtures of aqueous trifluoroacetic acid - acetonitrile followed by evaporation of the appropriate fractions gave the above compound (103 mg) as a white solid.

Analysis for $C_{18}N_{21}N_5O_4S$ CF_3COOH (MW 517.48):

Calc'd.:	C, 46.42; H, 4.29; N, 13.53.
Found:	C, 46.88; H, 4.52; N, 13.24.

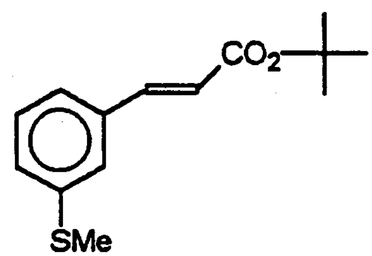
Example 245

Pr parati n of (±) β-[[2-[[[3-[(amin iminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-(methylthio)-benzenepropanoic acid, trifluoroacetate salt



Step A

1,1-dimethylethyl 3-[3-(methylthio)phenyl]-2E-propenoate



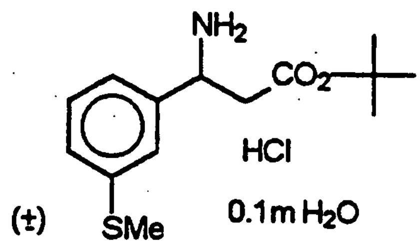
A solution of palladium acetate (110 mg, 0.00049 mole), 3-bromothioanisole (10 g, 0.05 mole), t-butylacrylate (7.7 g, 0.06 mole), tri-para-tolylphosphine (0.76 g, 0.0025 mole) and triethylamine (5.1 g, 0.05 mole) in 20 ml DMF was heated to 120°C for 20 hours. The solid was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated to an oily solid. Ethyl acetate was added and the solid was removed by filtration. The filtrate was concentrated to an oil. The product was purified by silica gel chromatography. The structure was support d by NMR.

Analysis Calc'd for $C_{14}H_{18}O_2S$ (250.36):

Calculated:	C, 67.16; H, 7.25.
Found:	C, 67.33; H, 7.24.

Step B

(±) 1,1-dimethylethyl β-amino-3-[3-(methylthio)phenyl]-propanoate, monohydrochloride



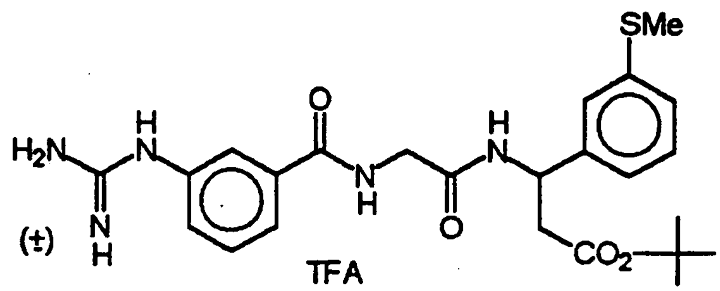
The product from Step A (10 g, 0.04 mole) was treated with t-BuOH saturated with ammonia and 1 ml acetic acid at 110°C and 900 psi in a Parr shaker for 78 hours. The mixture was filtered and concentrated to a dark oil. The product was purified by silica gel chromatography. A solution of the free base in 100 ml EtOAc was treated with 7N HCl in dioxane. The precipitate was filtered, washed with EtOAc and dried. The structure was supported by NMR.

Analysis calculated for $C_{14}H_{22}NO_2SCl \cdot 0.1\ H_2O$ (303.85 + 0.1 m H_2O):

Calculated:	C, 55.01; H, 7.32; N, 4.58.
Found:	C, 54.89; H, 7.36; N, 4.41.

Step C

(±) 1,1-dimethylethyl β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-3-(methylthio)phenylpropanoate, trifluoroacetate salt

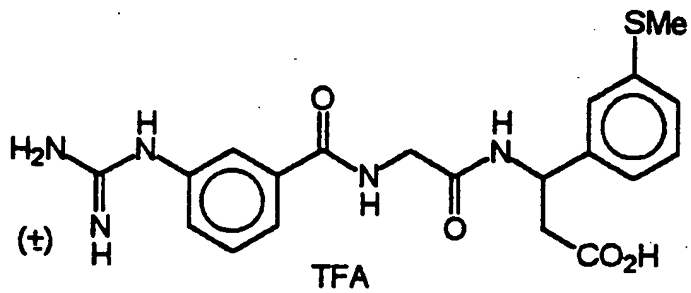


N-methylpiperidine (0.69 g, 0.007 mole) was added to the compound of Example M (0.91 g, 0.00334 mole) in 20 ml DMF at 0°C. A white solid precipitated. After 10 minutes IBCF (0.47 g, 0.00351 mole) was added. After 15 minutes (all in solution) a solution of the product from Step B (1.01 g, 0.00334 mole) in 6 ml DMF was added. The ice bath was removed and the solution was stirred at room temperature for 20 hours. The solution was concentrated to give an orange syrup. The product was purified by reverse phase HPLC. [CH_3CN/H_2O (0.06% TFA)]. The structure was supported by NMR.

Analysis calculated for $C_{24}H_{31}N_5O_4S$.TFA.1/2 H_2O (608.64)

Calculated:	C, 51.31; H, 5.47; N, 11.51
Found:	C, 51.46; H, 5.67; N, 11.51

Step D



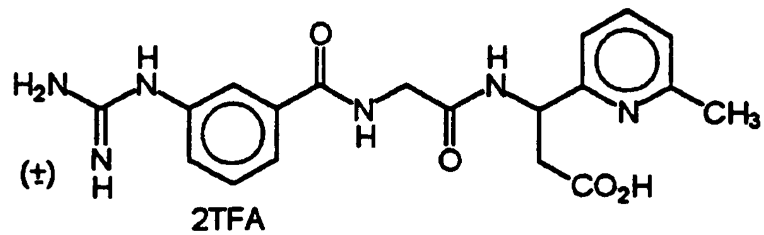
The product from Step C (0.50 g) in 10 ml CH_2Cl_2/TFA (1:1) was stirred for 24 hours at room temperature. After concentrating to a light yellow oil the product was purified by reverse phase HPLC (CH_3CN/H_2O.0.06% TFA). The structure was supported by NMR.

Analysis calculated for $C_{20}H_{23}N_5O_4S$.TFA.1/4 H_2O (548.03):

Calculated:	C, 48.22; H, 4.51; N, 12.78.
Found:	C, 48.19; H, 4.66; N, 12.80.

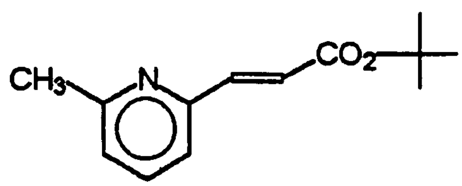
Example 246

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-6-methylpyridine-2-propanoic acid, bis(trifluoroacetate) salt



Step A

1,1-dimethylethyl 3-(6-methyl-2-pyridinyl)-2E-propanoate



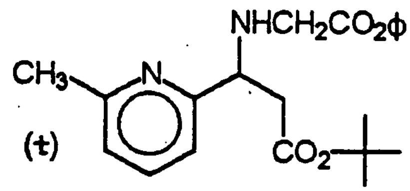
A solution of 6-methyl-2-pyridine carboxaldehyde (9.0 g, 0.074 mole) and (t-butylcarbonylmethylene)-triphenylphosphorane (28.0 g, 0.074 mole) in 150 ml toluene was heated to 85-90°C for 5 hours and stirred at room temperature for 20 hours. The white solid was removed by filtration and the filtrate was concentrated. Addition of 1:1 toluene/hexane (100 ml) precipitated more white solid which was removed by filtration. The filtrate was concentrated to an oil. The product was purified by silica gel chromatography. The structure was supported by NMR.

Analysis calc'd. for $C_{13}H_{17}NO_2$ (219.29):

Calculated:	C, 71.21; H, 7.81; N, 6.39.
Found:	C, 70.84; H, 7.81; N, 6.32.

Step B

(±) 1,1-dimethylethyl 6-methyl-β-[[(phenyloxycarbonyl)-methyl]amino]-pyridine-2-propanoat



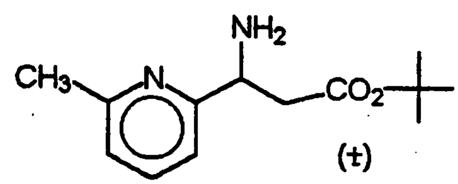
A solution of the product from Step A (5.0 g, 0.0228 mole) in benzylamine (48.9 g, 0.456 mole) was heated to 80°C for 6 hours and then at 100°C for 20 hours. The solution was heated at 115°C for 3 hours and then concentrated to an oil. The product was purified by silica gel chromatography. The structure was supported by NMR.

Analysis calc'd. for $C_{20}H_{26}N_2O_2$ (326.44):

	Calculated:	C, 73.59; H, 8.03; N, 8.58.
	Found:	C, 73.12; H, 8.14; N, 8.41.

Step C

(±) 1,1-dimethylethyl β-amino-6-methylpyridine-2-propanoate

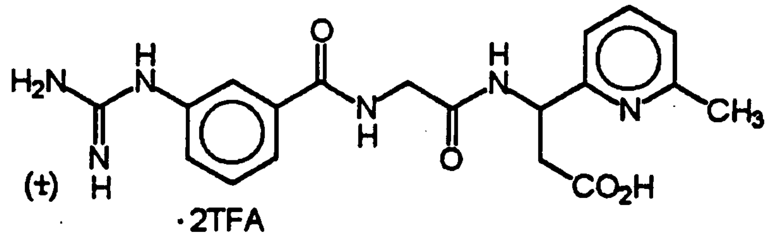


The product from Step B (5.7 g, 0.017 mole) in 3A-EtOH (100 ml) was treated with a catalytic amount of 4% Pd/C at 5 psi and room temperature for 48 hours. After filtration, the filtrate was concentrated to an oil. The product was purified by silica gel chromatography. The structure was supported by NMR.

Analysis calc'd. for $C_{13}H_{20}N_2O_2.0.3m\ H_2O$ (242.62):

Calculated:	C, 64.35; H, 8.60; N, 11.55.
Found:	C, 64.15; H, 8.38; N, 11.46.

Step D



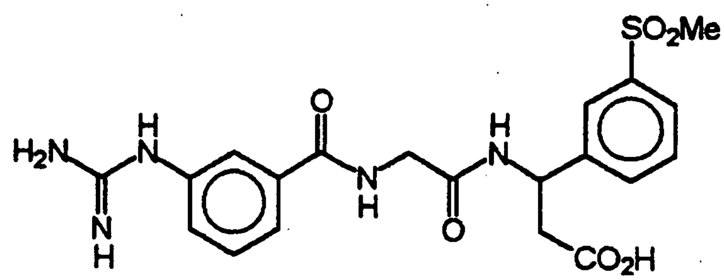
By following the reaction sequence described in Example 245, Steps C and D, and by the substitution of (±) 1,1-dimethylethyl β-amino-6-methylpyridine-2-propanoate for (±) 1,1-dimethylethyl β-amino-3-(methylthio)phenylpropanoate the title compound was prepared. The structure was supported by NMR.

Analysis calc'd. for $C_{23}H_{24}N_6O_8F_6$ (626.47):

Calculated:	C, 44.10; H, 3.86; N, 13.41.
Found:	C, 44.12; H, 3.70; N, 13.36.

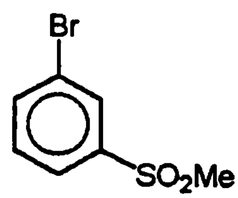
Example 247

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-(methylsulfonyl)-benzenepropanoic acid, bis(trifluoroacetate) salt



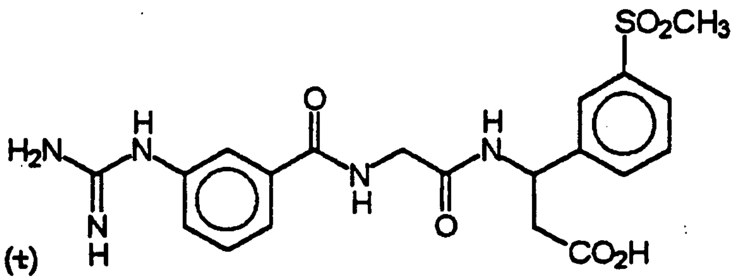
Step A

Methyl-3-bromophenylsulfone



A solution of Oxone® (90.8 g, 0.15 mole) in 250 ml H_2O was added to a stirring solution of 3-bromothioanisole (15 g, 0.0739 mole) in 250 mL MeOH and 200 ml acetone. The mixture was stirred at room temperature for 20 hours. The solution was concentrated to remove the MeOH and acetone. Water (400 ml) was added and the product extracted into EtOAc. The EtOAc was dried over Na_2SO_4, filtered and concentrated to give a solid. The structure was supported by NMR.

Step B



(t)

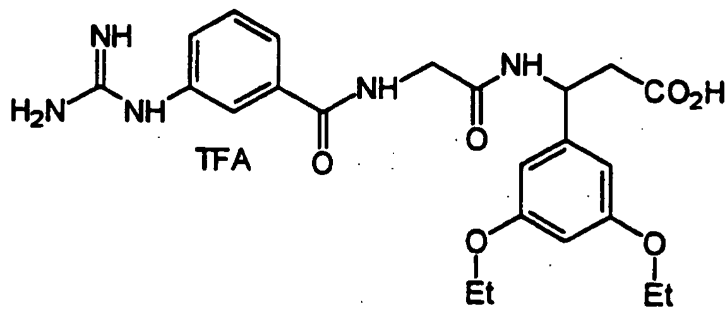
By following the reaction sequence described in Example 245, Steps A-D and by the substitution of methyl-3-bromophenyl sulfone for 3-bromothioanisole the title compound was prepared.

Analysis calc'd. for $C_{20}H_{23}N_5O_6S$.2TFA (689.55):

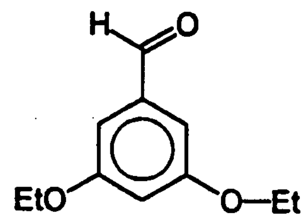
Calculated:	C, 41.81; H, 3.65; N, 10.16; S, 4.65.
Found:	C, 41.91; H, 3.74; N, 10.45; S, 5.15.

Example 249

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,5-diethoxybenzenepropanoic acid, trifluoroacetate salt

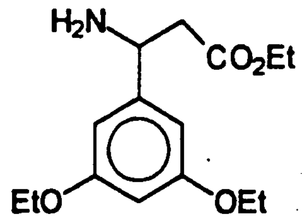


Step A



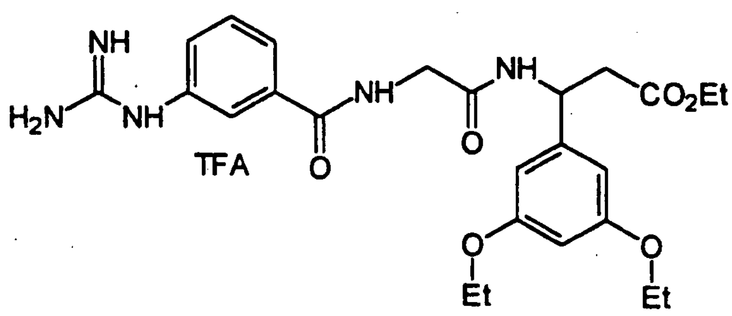
To 3,5-dihydroxybenzaldehyde (10 g) in DMF (100 mL) was added K_2CO_3 (20 g) and ethyliodide (20 g). The mixture was stirred for 3 days at 25°C. Water (250 mL) was added and the product extracted into ethyl acetate. The organic layer was separated, washed with water, brine and dried over Na_2SO_4 to give 3,5-diethoxyphenylcarboxaldehyde (12 g) as a dark oil. This material was used as is for the next step. MS and H-NMR were consistent with the proposed structure.

Step B



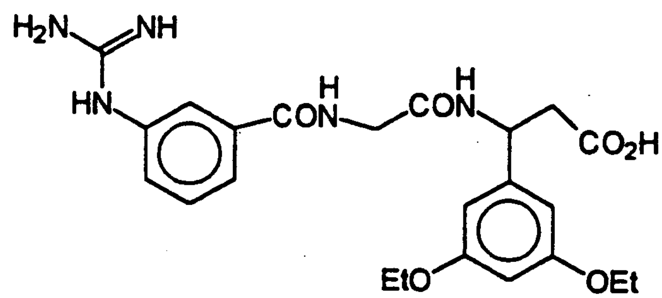
To 3,5-diethoxyphenylcarboxaldehyde (Step A) (10 g) in ethanol (70 mL) was added ammonium acetate (12.5 g) followed by ethyl hydrogen malonate (6.0 g). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(3,5-diethoxyphenyl) propionate as an oil. Ether (100 mL) was added, followed by HCl in dioxane (20 mL, 4N) and stirred vigorously for one hour. The HCl salt was collected by filtration (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step C



N,N'-Disuccinimidyl carb nate (DSC) (1.0 g, 0.4 mm l) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylf rmamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes, DL ethyl-3-amino-3-(3,5-diethoxyphenyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

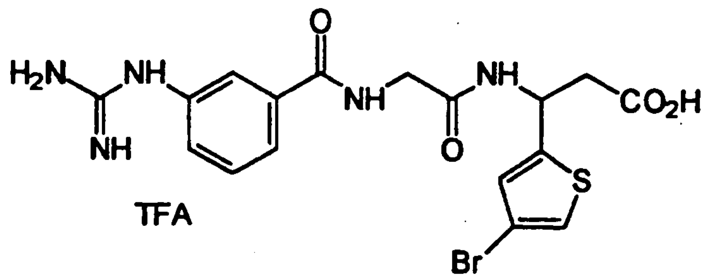
Step D



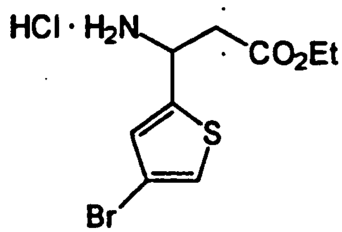
DL-ethyl 3-amino-3-(3,5-diethoxyphenyl) propionate adduct (500 mg) produced in Step C was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 250

Preparation f β-[[2-[[[3-[(aminoimin methyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-bromothiophene-2-propanoic acid, trifluoroacetate salt

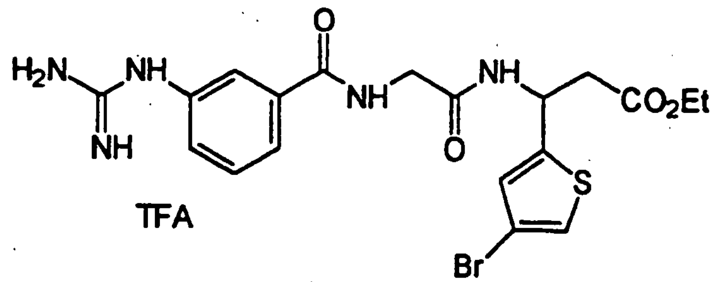


Step A



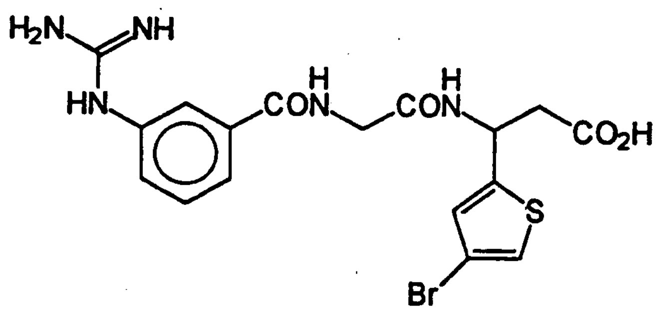
To 3-bromothiophene-5-carboxaldehyde (Aldrich) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(3-bromothiophene)propionate as an oil. Ether (100 mL) was added, followed by HCl in dioxane (20 mL, 4N) and stirred vigorously for one hour. The HCl salt was collected by filtration (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to compound H in Scheme VII (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(3-bromothiophene) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with proposed structure.

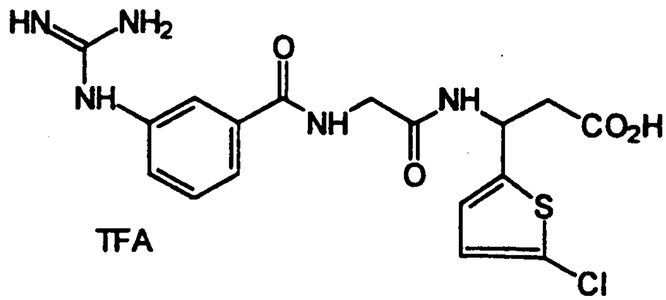
Step C



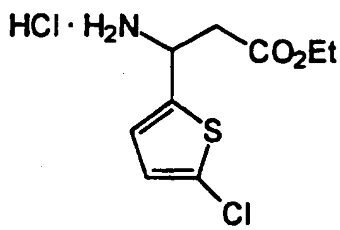
DL ethyl 3-amino-3-(3-bromothiophene) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 251

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-chlorothiophene-2-propanoic acid, trifluoroacetate salt

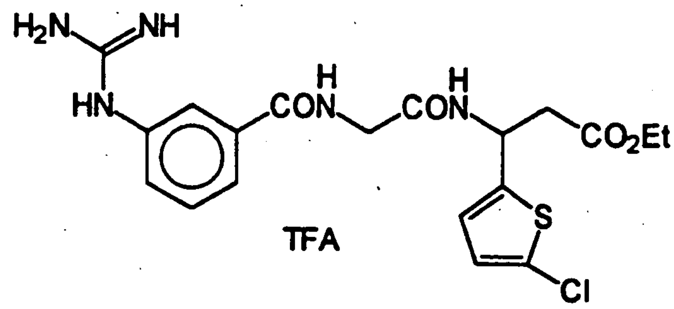


Step A



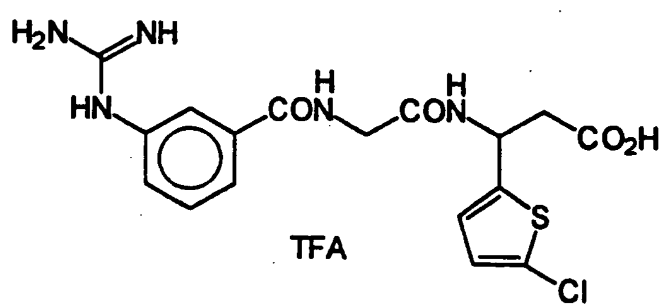
To 2-chlorothiophene-5-carboxaldehyde (Aldrich)(10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(2-chlorothiophene) propionate as an oil. Ether (100 mL) was added, followed by HCl in dioxane (20 mL, 4N) and stirred vigorouosly for one hour. The HCl salt was collected by filtration (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2-chlorothiophene) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

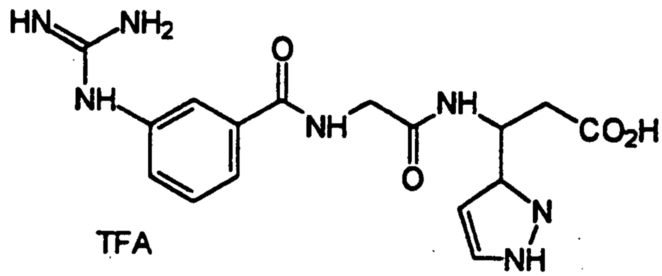


DL-ethyl 3-amino-3-(2-chlorothiophene) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete

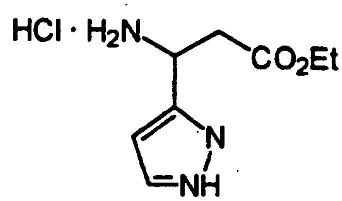
hydrolysis (1-2 h urs) triflu r acetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with proposed structure.

Example 252

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-1H-pyrazole-3-propanoic acid, trifluoroacetate salt

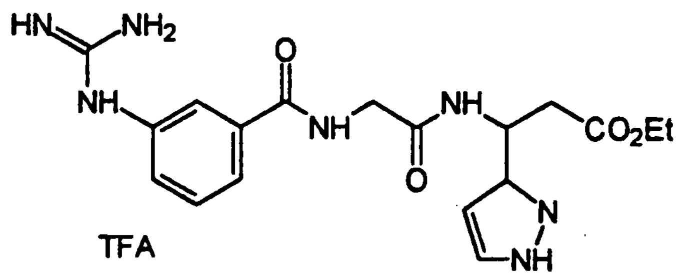


Step A



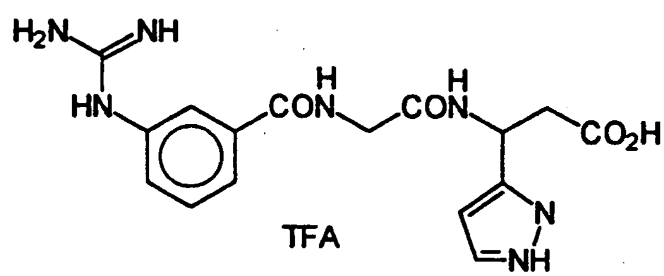
To 3-pyrazole carboxaldehyde (Maybridge) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(3-pyrazole) propionate as an oil. Ether (100 mL) was added, followed by HCl in dioxane (20 mL, 4N) and stirred vigorouosly for one hour. The HCl salt was collected by filtration (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to compound H in Scheme VII (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(3-pyrazole) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

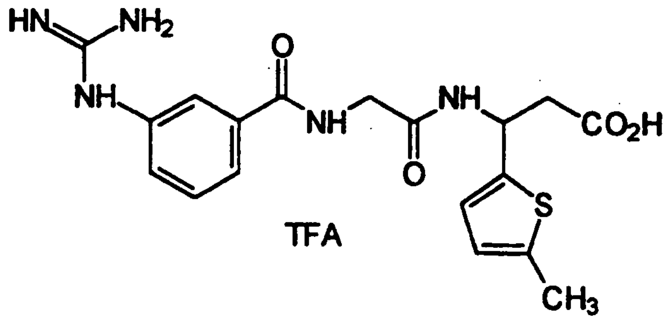


DL-ethyl 3-amino-3-(3-pyrazole) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added

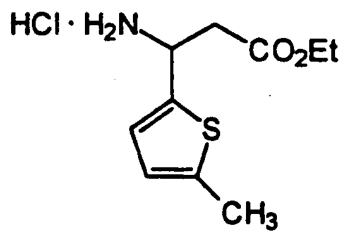
until pH = 2. Th product was purified by reverse phase chromatography (water/acetonitrile) t result in 255 mg of the title comp und as a white solid. MS and H-NMR were consistent with proposed structure.

Example 253

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-methylthiophene-2-propanoic acid, trifluoroacetate salt

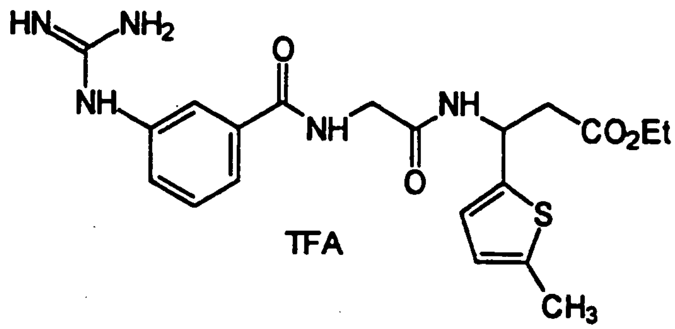


Step A



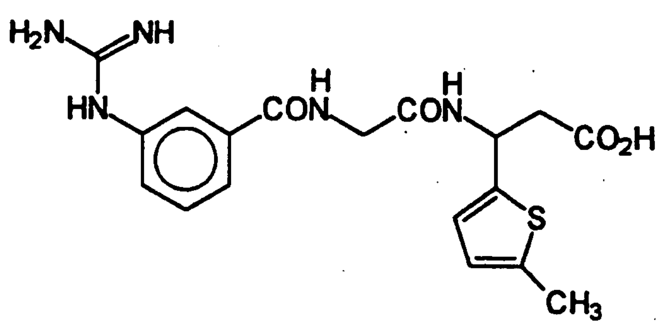
To 5-methythiophene-2-carboxaldehyde (Lancaster) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(5-methythiophene) propionate as an oil. Ether (100 mL) was added, followed by HCl in dioxane (20 mL, 4N) and stirred vigorouosly for one hour. The HCl salt was collected by filtration (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(5-methythiophene) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

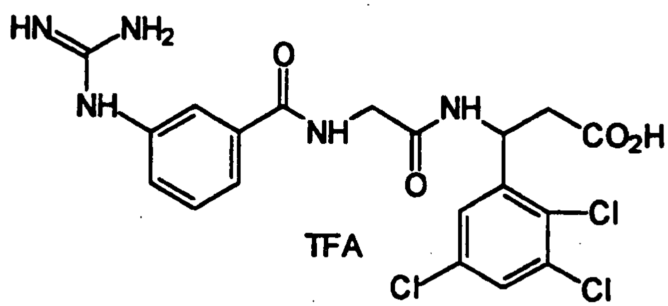


DL-ethyl 3-amino-3-(5-methythiophene) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to

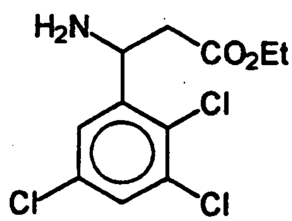
stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) triflu roac tic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 254

Preparation f β-[[2-[[[3-[(aminoiminom thyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-2,3,5-trichloro-benzenepropanoic acid, trifluoroacetate salt

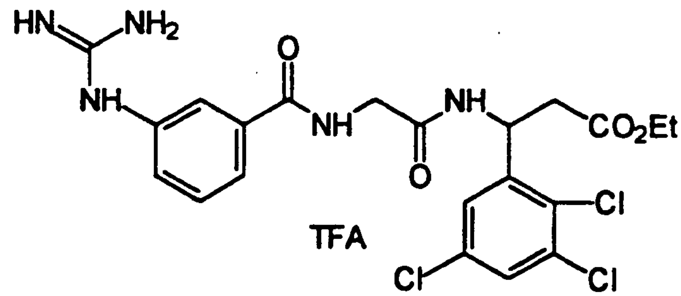


Step A



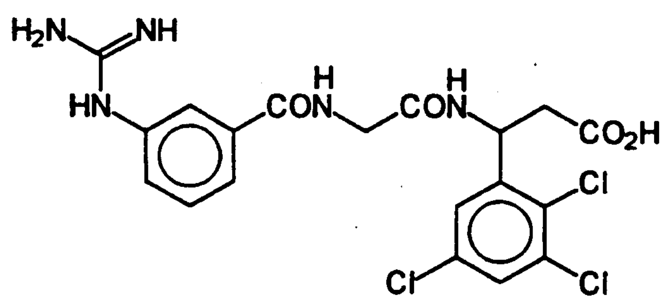
To 2,3,5-trichlorobenzaldehyde (Lancaster) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(2,3,5-trichlorophenyl) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2,3,5-trichlorophenyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

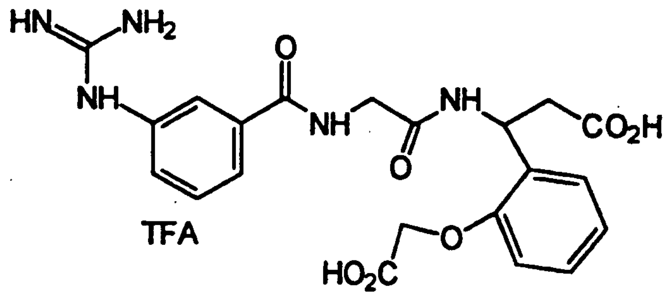


DL-ethyl 3-amino-3-(2,3,5-trichlorophenyl) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After compl te

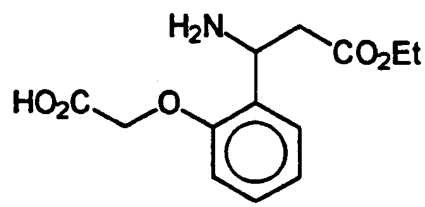
hydr lysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 255

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-2(carboxymethoxy)-benzenepropanoic acid, trifluoroacetate salt

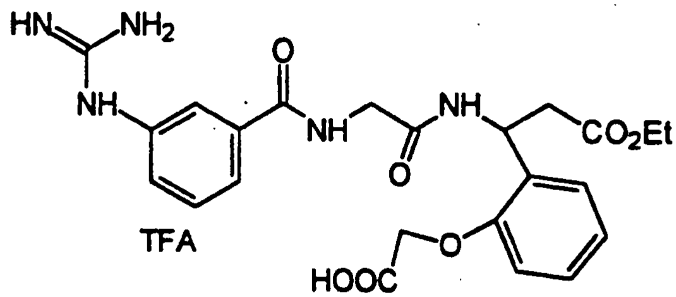


Step A



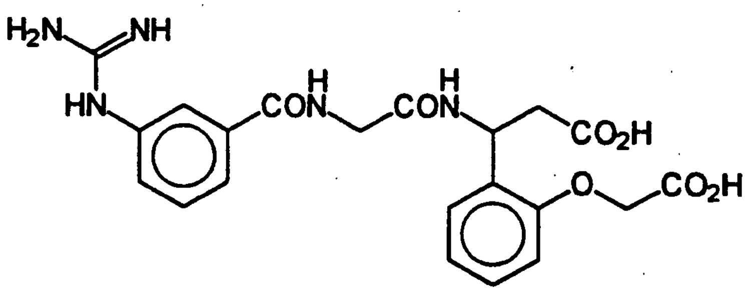
To 2-formyl phenoxyacetic acid (Fisher) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was filtered to give DL ethyl-3-amino-3-(2-formyl phenoxyacetic acid) propionate as a solid (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2-formyl phenoxyacetic acid) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

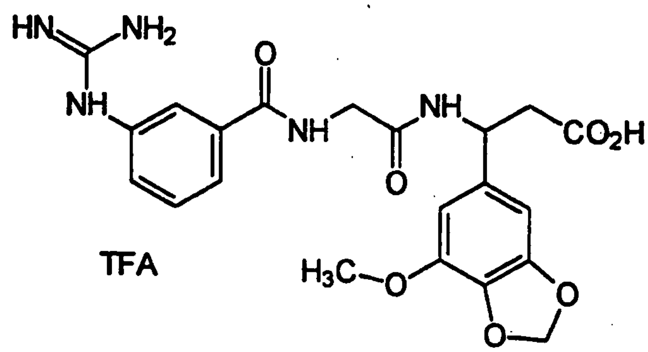


DL-ethyl 3-amino-3-(2-formyl phenoxyacetic acid) propionate adduct produced in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After

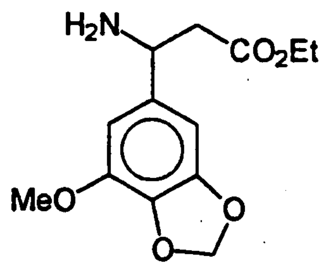
complete hydrolysis (1-2 hours) trifluoroacetic acid was add d until pH = 2. The product was purified by r verse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 256

Preparati n f β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4-methoxy-1,3-benzodioxole-6-propanoic acid, trifluoroacetate salt

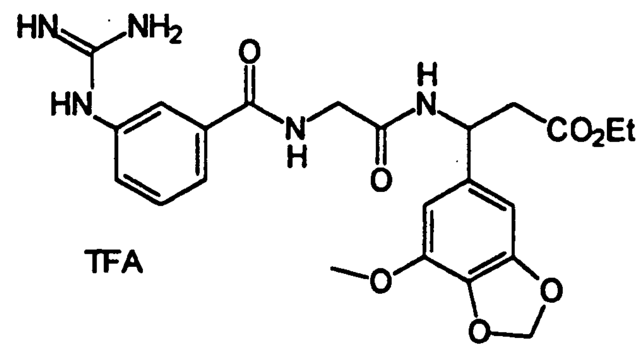


Step A



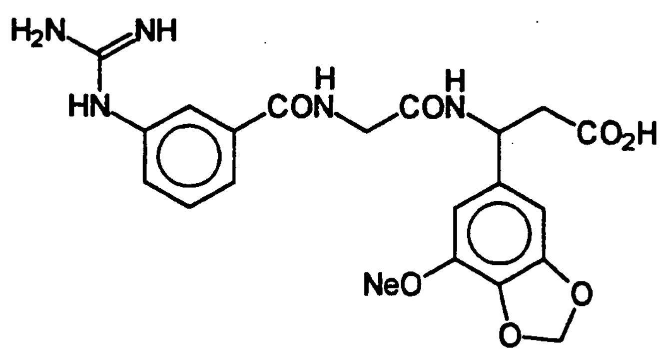
To 2-methoxy piperinal (Fisher) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(2-methoxy piperinal) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2-methoxy piperinal) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

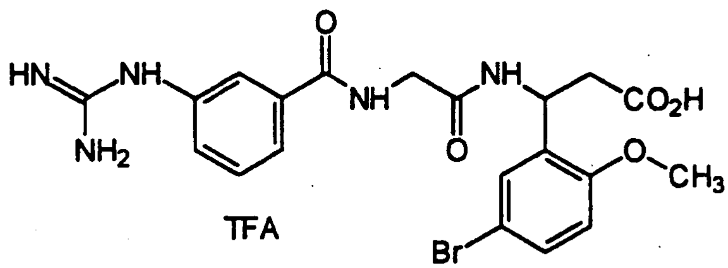


DL-ethyl 3-amino-3-(2-methoxy piperinal) propionate adduct prepared in Step B (500 mg) was dissolved in water/ac tonitrile ((1:1)), followed by the addition of

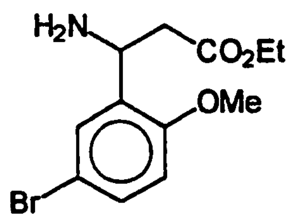
lithium hydroxide (100 mg). The reaction was allow d to stir at 25°C, and monitored by HPLC. After c mplete hydrolysis (1-2 hours) trifluor acetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 257

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-5-bromo-2-methoxybenzenepropanoic acid, trifluoroacetate salt

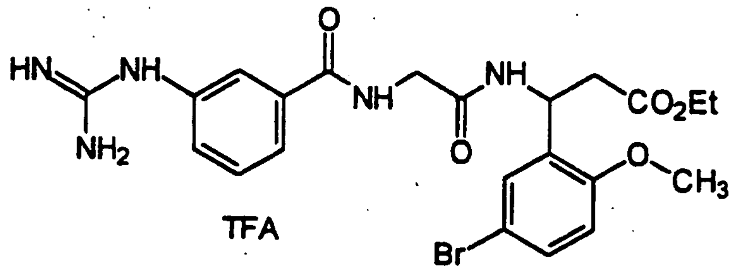


Step A



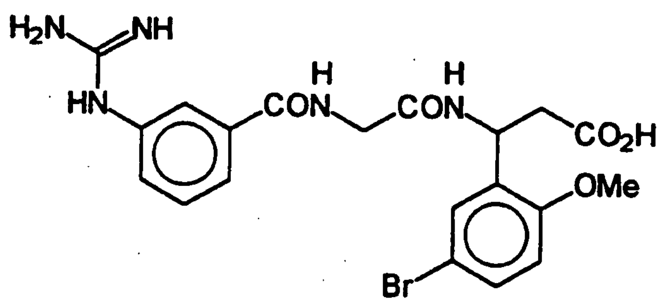
To 3-bromo-6-methoxybenzaldehyde (Aldrich) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(3-bromo-6-methoxyphenyl) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(3-bromo-6-methoxyphenyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

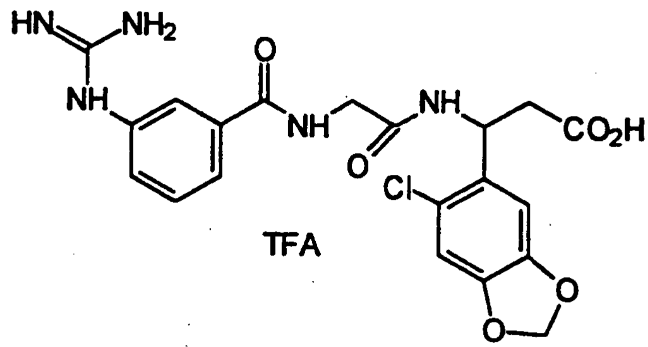


DL-ethyl 3-amino-3-(3-bromo-6-methoxyphenyl) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile ((1:1)), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was

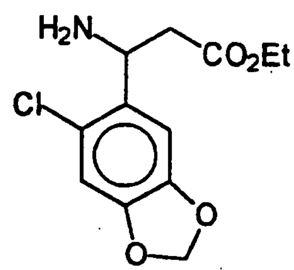
added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the titl compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 258

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-6-chloro-1,3-benzodioxole-5-propanoic acid, trifluoroacetate salt

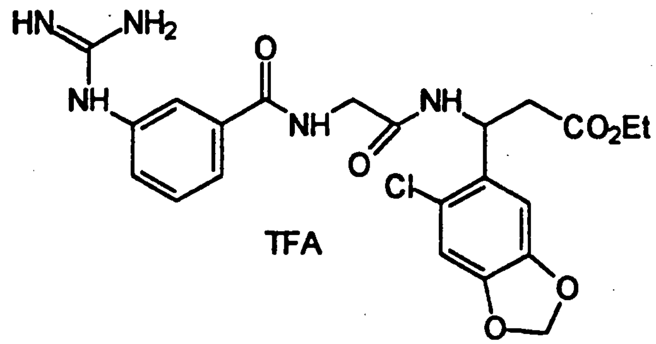


Step A



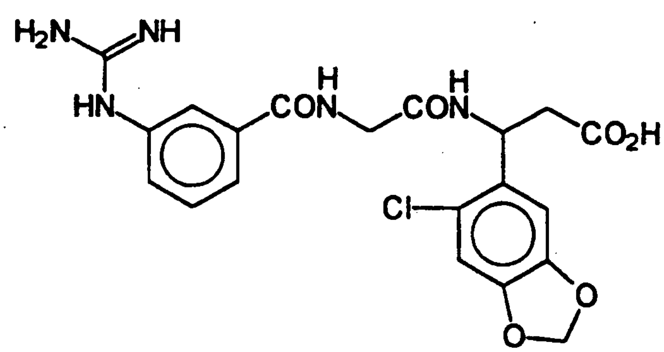
To 6-chloropiperinal (Lancaster) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(6-chloropiperinyl) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(3-chloropiperinyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

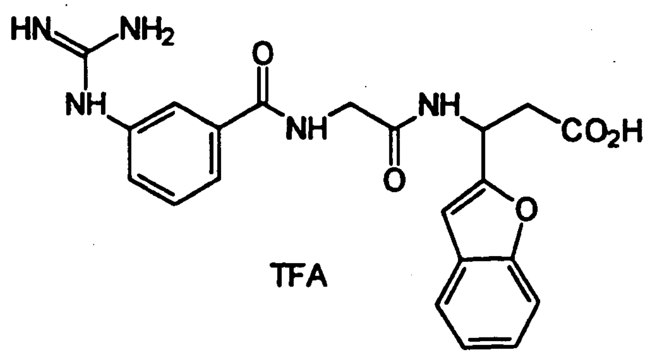


DL-ethyl 3-amino-3-(6-chloropiperinyl) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition f

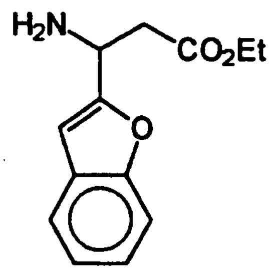
lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitor d by HPLC. After c mplete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 259

Preparati n f β-[[2-[[[3-[(amin iminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-benzofuran-2-propanoic acid, trifluoroacetate salt

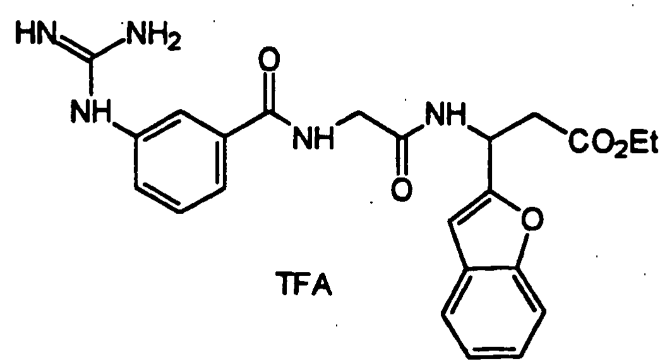


Step A



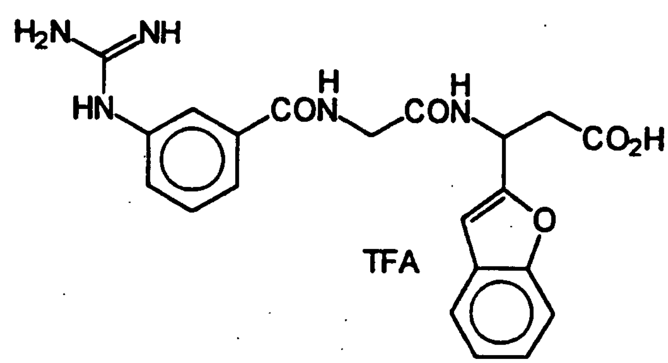
To 2-benzofuran carboxaldehyde (Lancaster) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(2-benzofuranyl) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structur .

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2-benzofuranyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

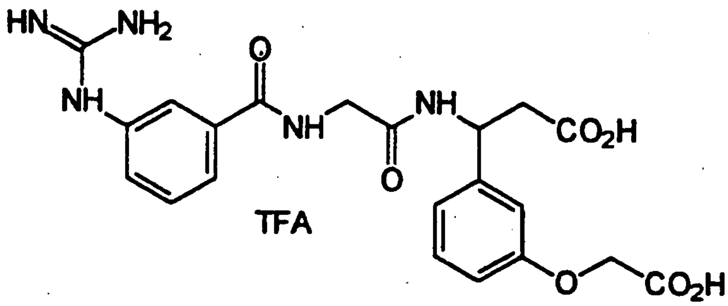


DL-ethyl 3-amino-3-(2-benzofuranyl) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of

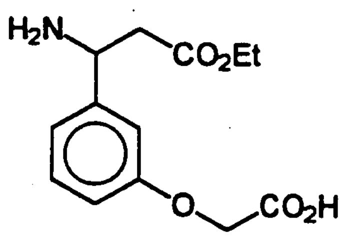
lithium hydroxid (100 mg). The reaction was allowed to stir at 25°C, and m nit red by HPLC. After compl te hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 260

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-(carboxymethoxy)benzenepropanoic acid, trifluoroacetate salt

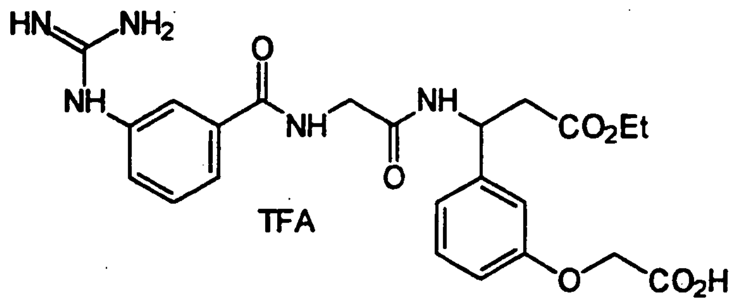


Step A



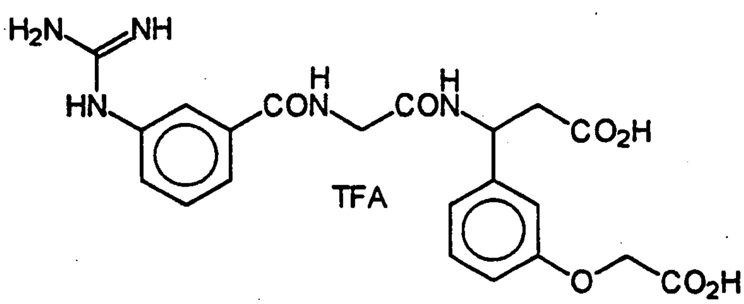
To 3-formyl phenoxyacetic acid (Fisher) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was filtered to give DL ethyl-3-amino-3-(3-formyl phenoxyacetic acid) propionate as an oil (6.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N′-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(3-formyl phenoxyacetic acid) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

Step C

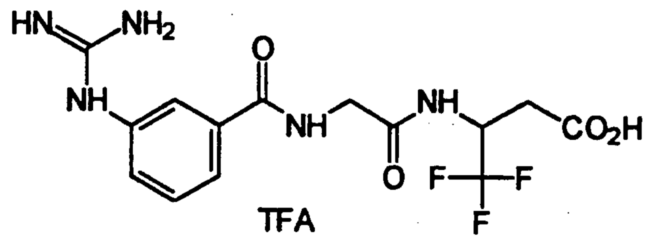


DL ethyl 3-amino-3-(3-formyl phenoxyacetic acid) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was

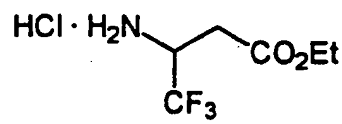
allowed to stir at 25°C, and m nitored by HPLC. After c mplete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. Th product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 261

Preparation of 3-[[2-[[[3-[(aminoiminom thyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-4,4,4-trifluorobutanoic acid, trifluoroacetate salt

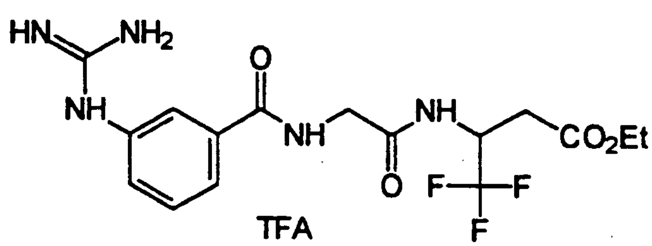


Step A



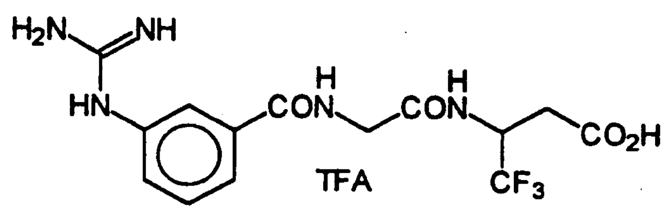
To 3-amino-4,4,4-trifluorobutyric acid (Lancaster) (2 g) in ethanol (70 mL) was added HCl in dioxane (20 mL, 4N) and stirred vigorously for 16 hours. The solvent was removed under reduced pressure. The HCl salt was collected as a solid (2.3 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonat (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(4,4,4-trifluoro) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

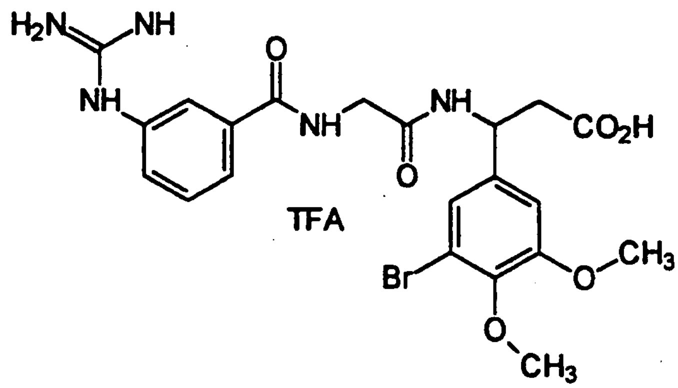
Step C



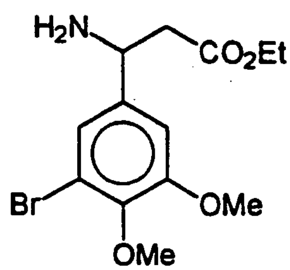
DL-ethyl 3-amino-3-(4,4,4-trifluoro) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 262

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3-bromo-4,5-dimethoxybenzenepropanoic acid, trifluoroacetate salt



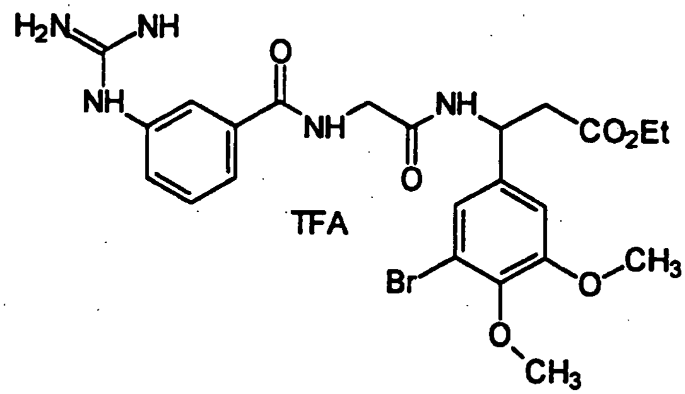
Step A



To 3-bromo-4,5-dimethoxy benzaldehyde (Aldrich) (10 g) in ethanol (70 mL) was added ammonium acetate (2.5 equivalents) followed by ethyl hydrogen malonate (1.1 equivalents). The reaction mixture was stirred at reflux for 5 hours. The solution was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. The organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporat d to give DL ethyl-

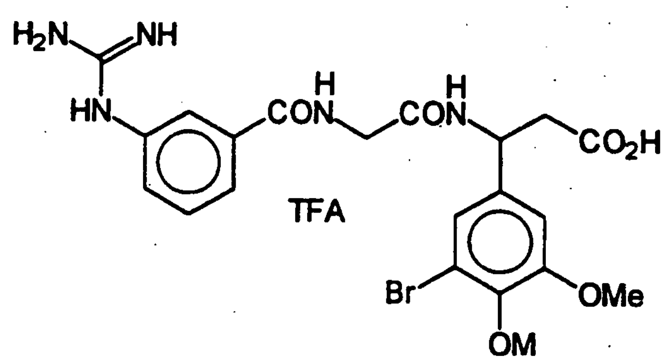
3-amino-3-(3-bromo-4,5-dimeth xyphenyl) propionat as an oil (6.3 g). MS and H-NMR w re c nsistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(2-bromo-4,5-dimethoxyphenyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

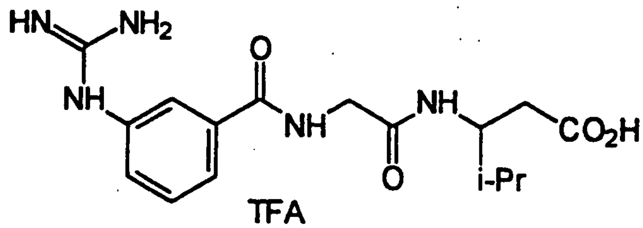
Step C



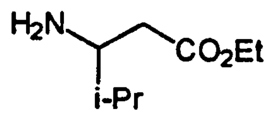
DL-ethyl 3-amino-3-(3-bromo-4,5-dimethoxyphenyl) pr pionate adduct prepared in Step B (500 mg) was diss lved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 263

Preparation of 3-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-4-methylpentanoic acid, trifluoroacetate salt

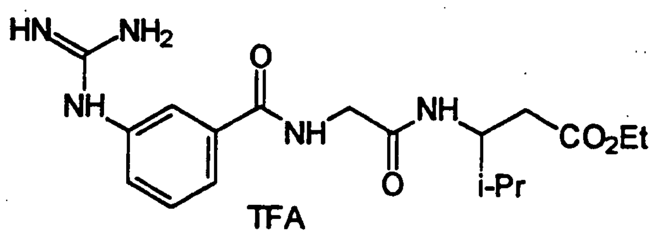


Step A



DL ethyl-3-amino-3-(isopropyl) propionate was prepared by the method of Example 53, Step A substituting isopropylacetoacetate (10 g) for dimethyl-3-ketoglutarate. MS and H-NMR were consistent with the proposed structure.

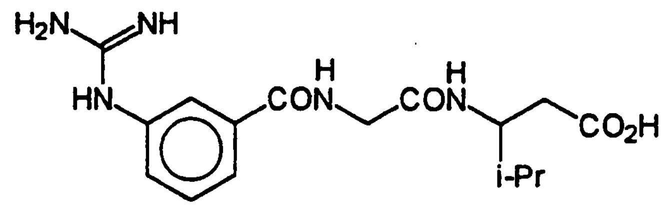
Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(isopropyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by

reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

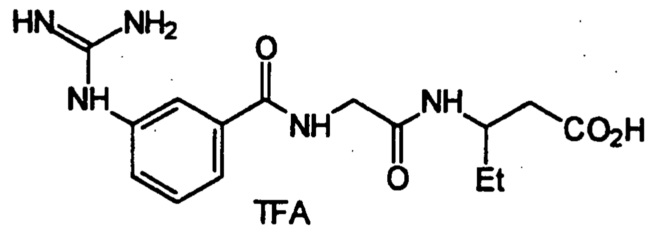
Step C



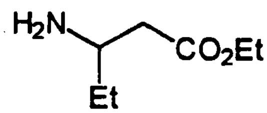
DL ethyl 3-amino-3-(isopropyl) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 264

Preparation f 3-[[2-[[[3-[(aminoiminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-pentanoic acid, trifluoroacetate salt

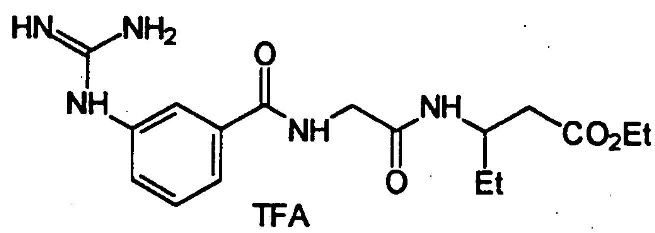


Step A



DL ethyl-3-amino-3-(3-ethyl) propionate was prepared by the method of Example 53. Step A, substituting ethylacetoacetate (10 g) for dimethyl-3-ketoglutarate. MS and H-NMR were consistent with the proposed structure.

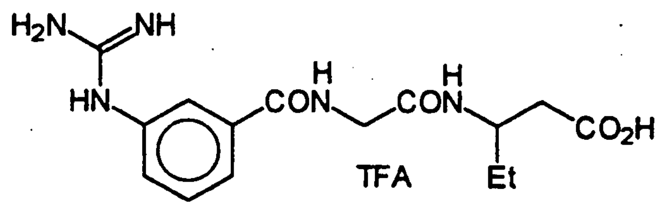
Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl-3-amino-3-(ethyl) propionate (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete

reaction (1-16 hours) the product was purified by rev rse phas chromatography (water/acetonitril) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

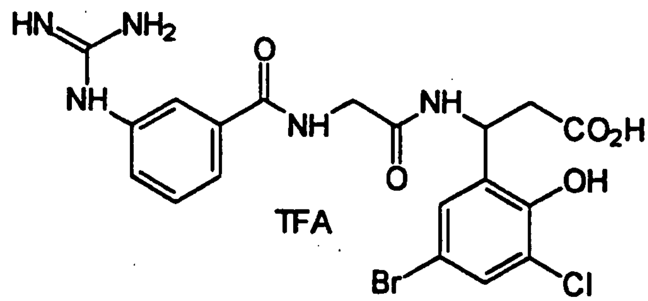
Step C



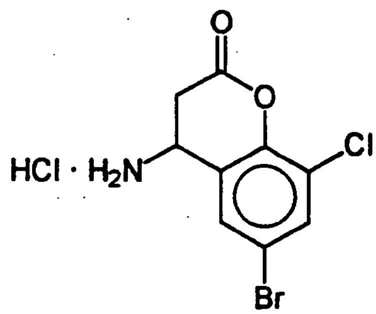
DL-ethyl 3-amino-3-(ethyl) propionate adduct prepared in Step B (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 265

Preparati n of β-[[2-[[[3-[(amin iminomethyl)-amino]phenyl]carbonyl]amino]acetyl]amino]-5-bromo-3-chloro-2-hydroxybenzene-propanoic acid, trifluoroacetate salt

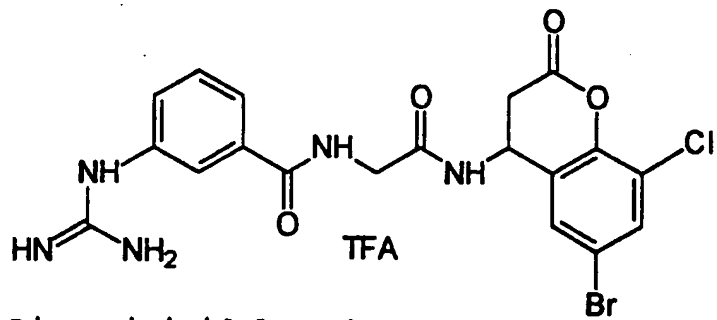


Step A



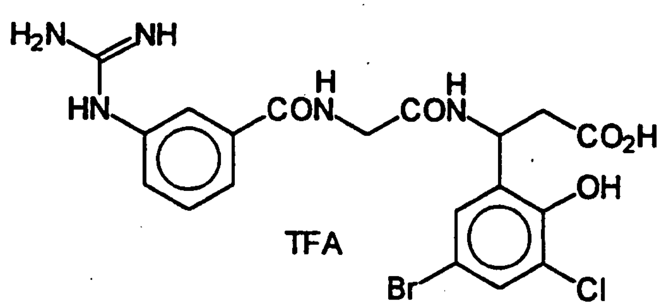
DL-3-bromo-5-chloro-2-hydroxy aminocoumarin hydrochloride was prepared according to Scheme XIV. The method of G. Casiraghi, et al. J. Chem. Soc. Perkin Trans 1 p.318, 1978, was employed for the preparation of the 4-bromo-2-chlorosalicylic aldehyde and 6-bromo-8-chloro-coumarin was prepared by the method of Vogel's The Textbook of Practical Organic Chemistry, fifth edition p. 1040. The amino coumarin was prepared by the method cited in Example 87 using 7-chloro-5-bromo coumarin (7 g). MS and H-NMR were consistent with the proposed structure.

Step B



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by dimethylaminopyridine (100 mg). After a period of 20 minutes DL-3-bromo-5-chloro-2-hydroxy aminocoumarin hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

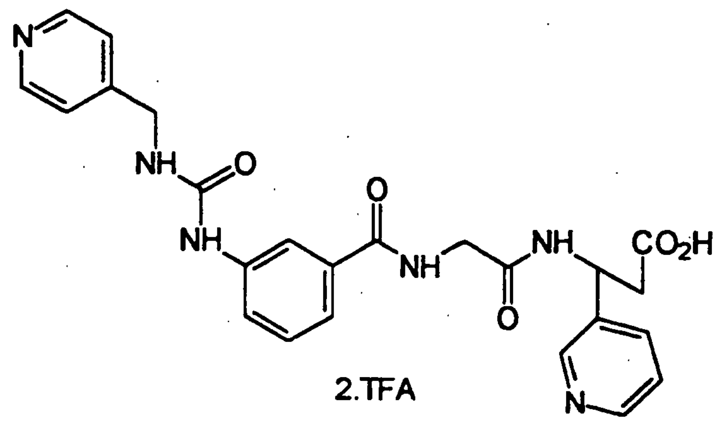
Step C



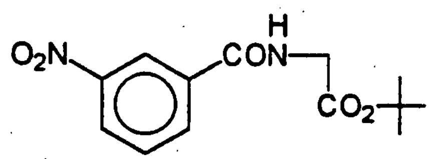
DL-3-bromo-5-chloro-2-hydroxy aminolactone adduct prepared in Step B (500 mg) dissolved in water/acetonitrile slowly opened to form a (2-hydroxy acid) resulting in 255 mg of the title compound as a white solid after purification by reverse phase chromatography and lyophylization as its TFA salt. MS and H-NMR were consistent with the proposed structure.

Example 266

Preparation of β-[[2-[[[3-[[[(4-pyridinylmethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, (bis)trifluoroacetate salt

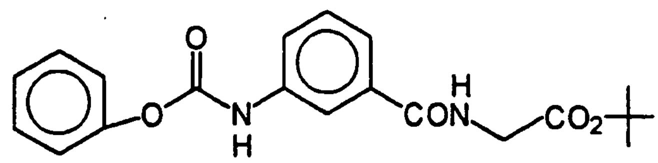


Step A



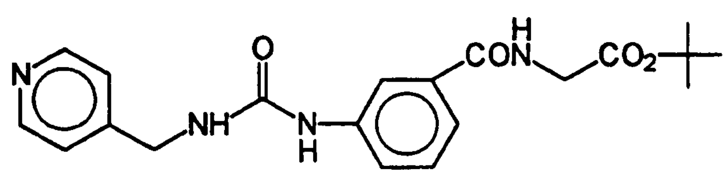
Glycine tert-butyl ester (20 g, 119 mmol) was added to water (200 mL) followed by potassium carbonate (20 g, 180 mmol) and cooled to 0°C in an ice bath. To this solution 3-nitrobenzoyl chloride (20 g, 108 mmol) was added in acetonitrile (20 mL) drop-wise over a 10 minute period. After complete reaction (3-4 hours) concentrated hydrochloric acid was added until pH=3 followed by saturated aqueous NaCl (75 mL). The product was filtered, washed with water and air dried (22 g, 90% yield). MS and H-NMR were consistent with the proposed structure.

Step B



tert-Butyl(3-nitrobenzoyl) glycinate (1.0 g) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (1 mg) was added and the mixture was hydrogenolyzed under 50 psi in a Parr apparatus for a period of 2.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried *in vacuo*. Dimethylformamide (25 mL) was added to the crude aniline tert-butyl ester followed by triethylamine (1.5 equivalents) and cooled to 0°C. Phenyl chloroformate (6.5 g, 1.1 equivalents) was added and the reaction stirred for 2 hours. Water was added and the solid was filtered to give the phenyl carbamate tert-butyl ester as a white solid (12.5 g, 99% yield). MS and H-NMR were consistent with the proposed structure.

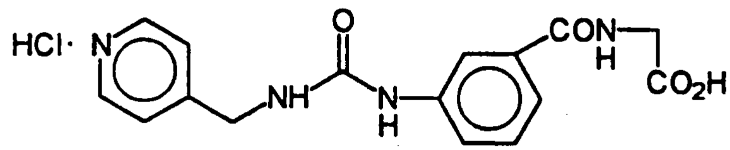
Step C



Dimethylformamide (25 mL) was added to the phenyl carbamate tert-butyl ester from Step B followed by 4-pyridylmethylamine (1.1 equivalents). The reaction was heated at 70°C with stirring for 2 hours and stirred at 25°C for 12 hours. Water was added, and the mixture

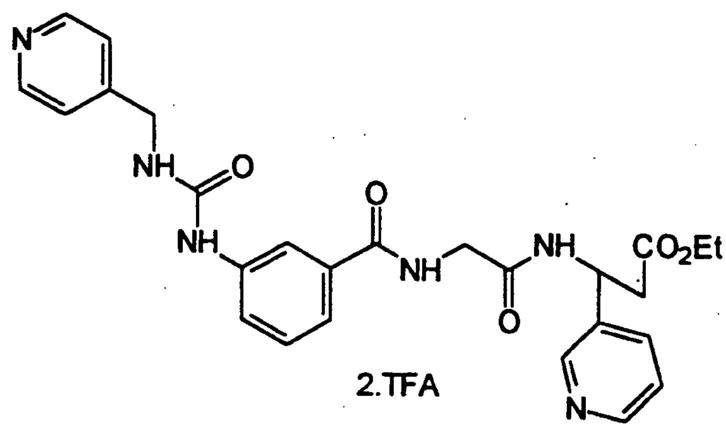
partition d between ethyl acetate, s parated and washed with brine and dried ver Na_2SO_4 to give an oil (6 g). MS and H-NMR were consistent with the proposed structure.

Step D



The compound from Step C (6 g) was dissolved in dioxane (25 mL). To this solution HCl in dioxane (20 mL, 4N) was added. The solution was stirred for 12 hours and the solvent was removed under reduced pressure followed by the addition of ether. The solid was filtered and dried in a vacuum oven for 12 hours.

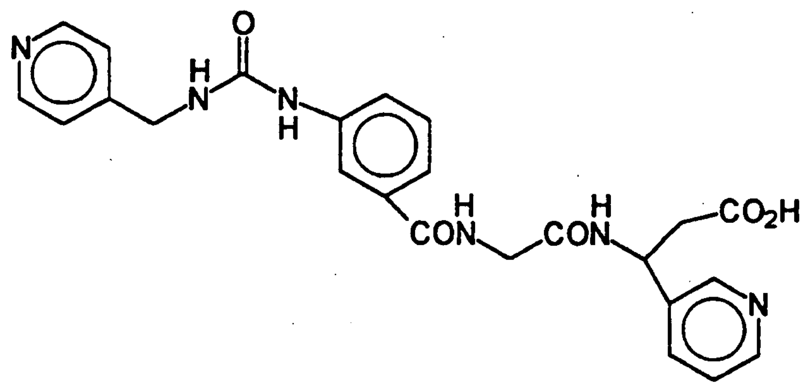
Step E



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step D (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL-ethyl 3-amino-3-pyridyl propionate

hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

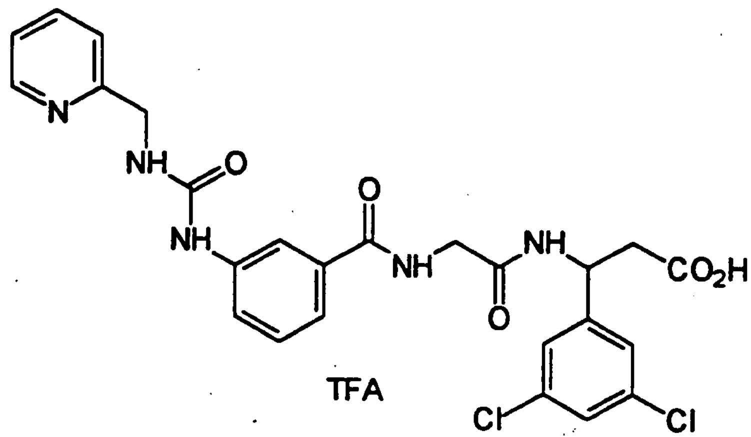
Step F



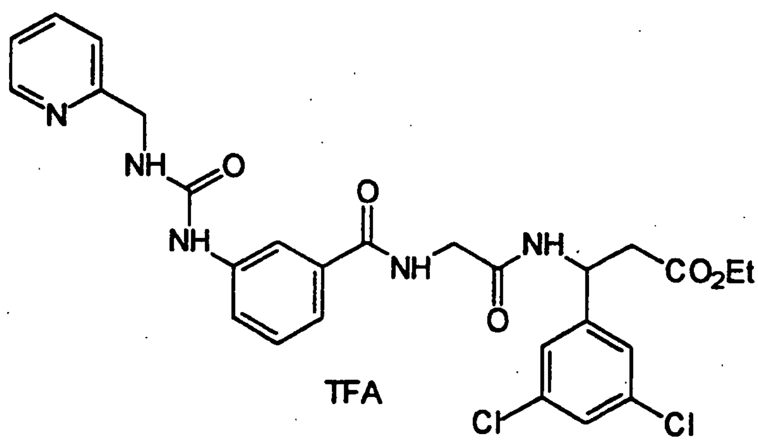
DL-ethyl 3-amino-3-pyridyl propionate adduct produced in Step E (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 255 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 267

Preparation of 3,5-dichlor -β-[[2-[[[3-[[[(4-pyridinylmethyl)amino]carbonyl]amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid, trifluoroacetate salt



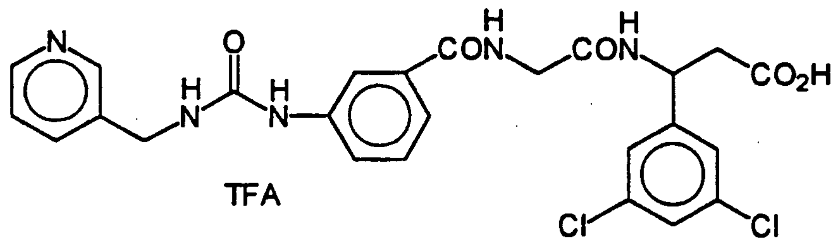
Step A



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B, Example 268 (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate hydrochloride (1.1 g, 0.5 mmol)

was added followed by NMM (2.0 mL). After complet reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.0 g). MS and H-NMR were consistent with the proposed structure.

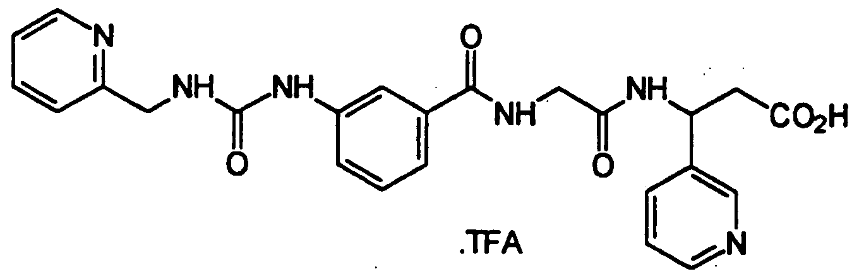
Step B



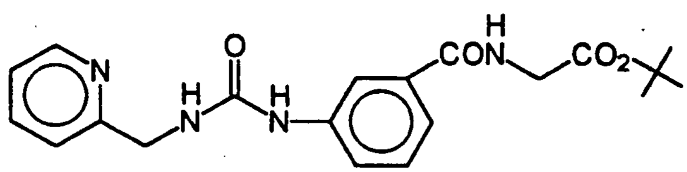
DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate adduct produced in Step A (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 315 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 268

Preparation of β-[[2-[[[3-[[[(2-pyridinylmethyl)amino]-carbonyl]amino]phenyl]carbonyl]amino]acetyl]amino]-pyridine-3-propanoic acid, (bis)trifluoroacetate salt

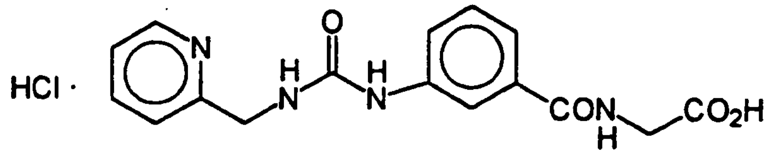


Step A



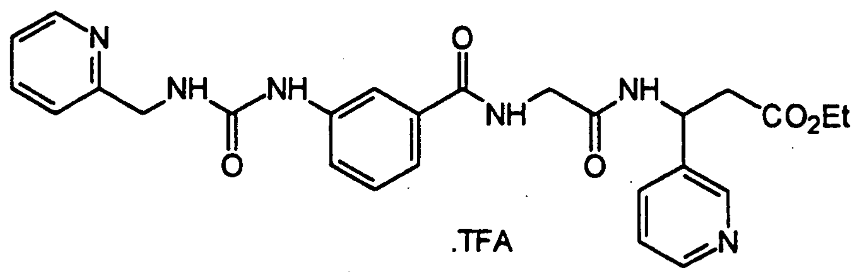
Dimethylformamide (25 mL) was added to the phenyl carbamate tert-butyl ester from Example 266, Step B, followed by 2-pyridylmethylamine (1.1 equivalents.) and the reaction was heated at 70°C with stirring for 2 hours and stirred at 25°C for 1- 2 hours. Water was added and the mixture partioned between ethyl acetate, separated, washed with brine and dried over Na_2SO_4 to give an oil (6 g). MS and H-NMR were consistent with the proposed structure.

Step B



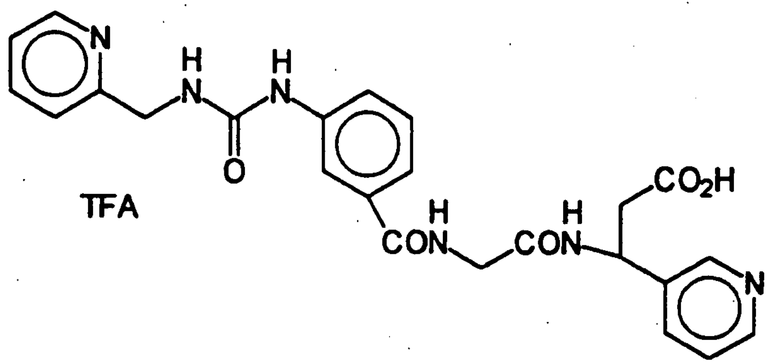
The compound produced in Step A (6g) was disolved in dioxane (25 mL). To this solution HCl in dioxane (20 mL, 4N) was added. The solution was stirred for 1-2 hours. The solvent was removed under reduced pressure followed by addition of ether. The solid was filtered and dried in a vacuum oven for 12 hours.

Step C



N,N'-Disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL-ethyl 3-amino-3-pyridyl propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hr) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.1 g). MS and H-NMR were consistent with the proposed structure.

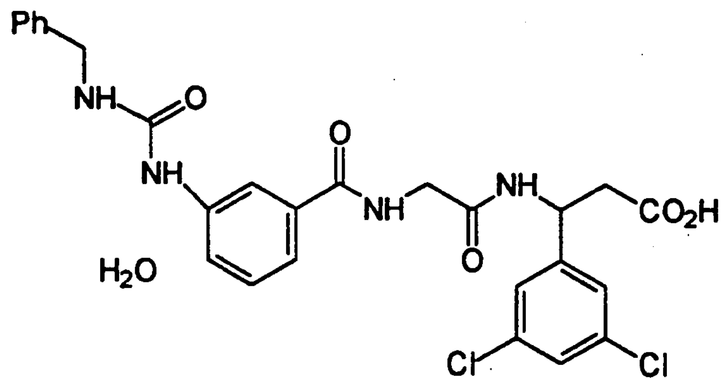
Step D



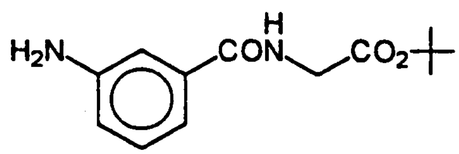
DL-ethyl 3-amino-3-pyridyl propionate adduct produced in Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 550 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 269

Preparation of 3,5-dichloro-β-[[2-[[[3-[[[(phenylmethyl)amino]carbonyl]amino]phenyl]-carbonyl]amino]acetyl]amino]benzenepropanoic acid, monohydrate

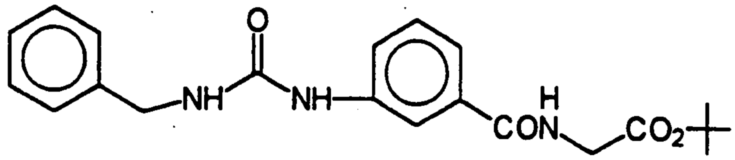


Step A



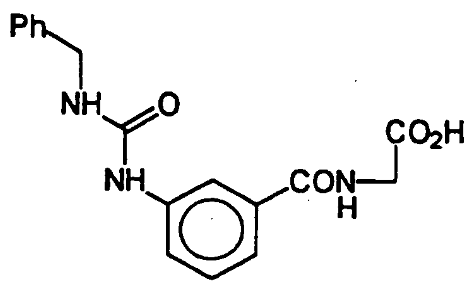
tert-butyl(3-nitrobenzoyl) glycinate (10 g) was added to absolute ethanol (60 mL) in a Parr jar. Palladium on carbon 5% (1 mg) was added and the mixture was hydrogenolyzed under 50 psi in a Parr apparatus for a period of 2.5 hours. After complete reaction the palladium catalyst was removed by filtration through a plug of celite. The solvent was removed under reduced pressure and the sample dried in vacuo.

Step B



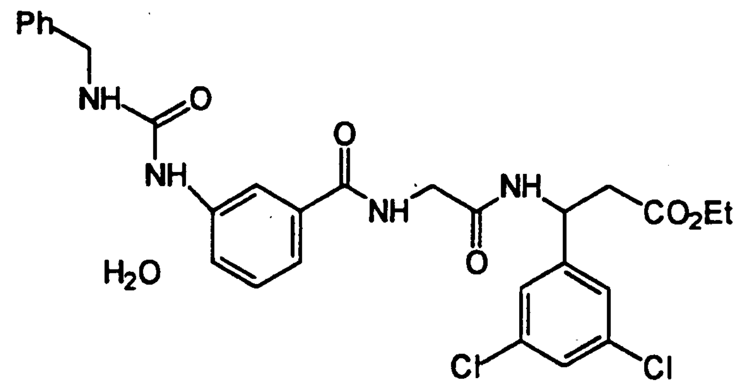
Acetonitrile (50 mL) was added to the crude aniline (10 g) produced in Step A followed by benzyl isocyanate (7.0 g). The solution was warmed to 70°C for 2 hours, and the solvent removed. Diethyl ether was added and the solid was filtered to give the benzyl urea tert-butyl ester as a salmon colored solid (12.6 g).

Step C



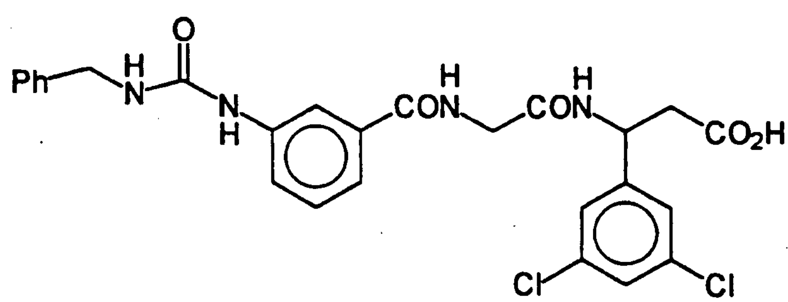
The compound produced in Step B (6 g) was disolved in dioxane (25 mL). To this solution HCl in dioxane (20 mL, 4N) was added. The solution was stirred for 12 hours and the solvent was removed under reduced pressure followed by addtion of ether. The solid was filtered and dried in a vacumn oven for 12 hours.

Step D



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to compound produced in Step C (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 min DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white solid (1.2 g). MS and H-NMR were consistent with the proposed structure.

Step E

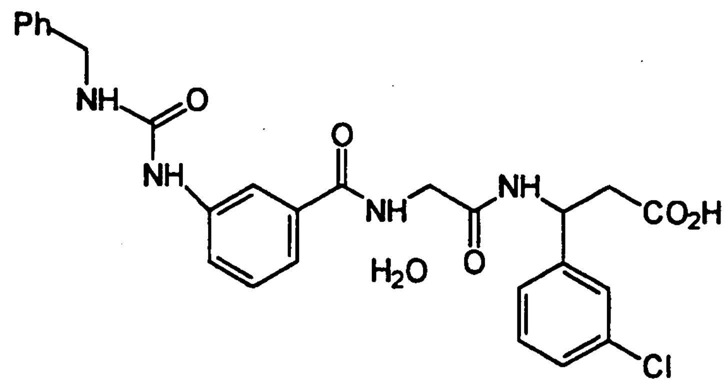


DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate adduct produced in Step D (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of

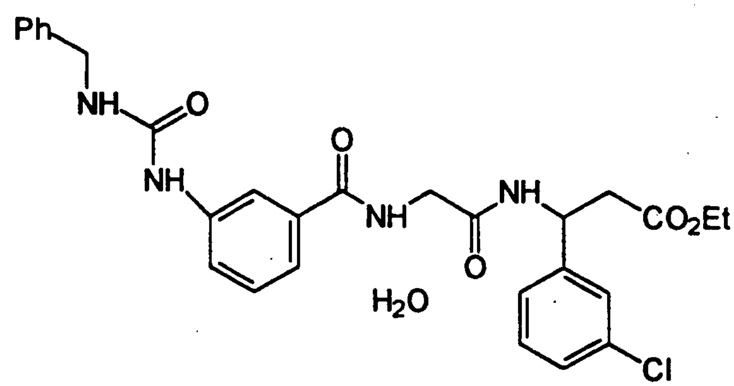
lithium hydroxide (100 mg). Th reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 250 mg of the title compound as a white solid. MS and H-NMR was consistent with the proposed structure.

Example 270

Preparation of 3-chloro-β-[[2-[[[3-[[[(phenylmethyl)amino]carbonyl]amino]phenyl]-carbonyl]amino]acetyl]amino]-benzenepropanoic acid, monohydrate



Step A



N,N′-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produce of Step C, Example 269 (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL-ethyl 3-amino-3-(3-chlorophenyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase

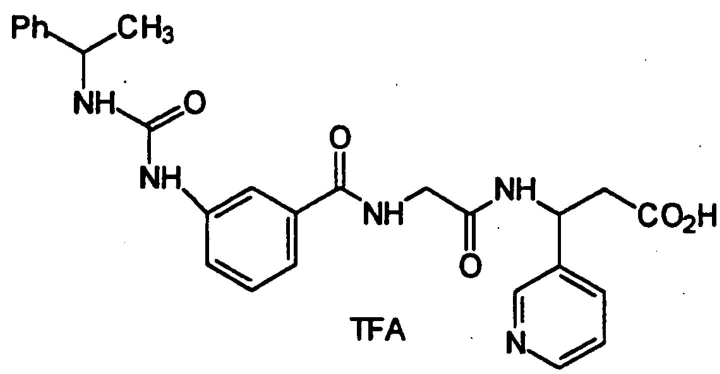
chromatography (water/acetonitrile) to result in a white solid (0.9 g). MS and H-NMR were c nsistent with the proposed structure.

Step B

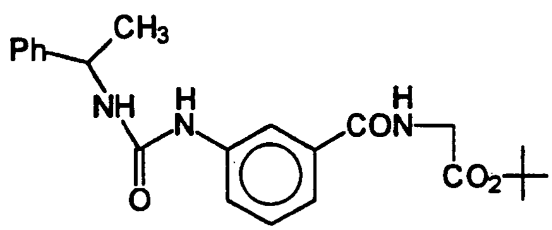
DL-ethyl 3-amino-3-(3-chlorophenyl) propionate adduct produced in Step A (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 350 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 271

Preparation of β-[[2-[[[3-[[[(1-phenylethyl)-amino]carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt

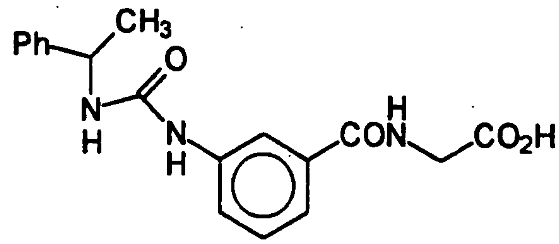


Step A



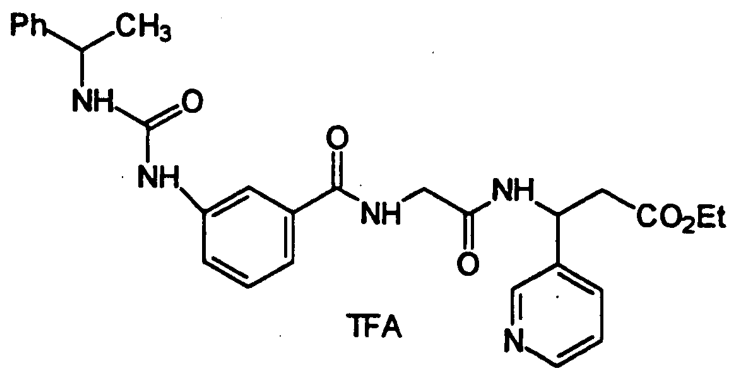
Dimethylformamide (25 mL) was added to the phenyl carbamate tert-butyl ester from Step B of Example 266 followed by α-methyl benzylamine (1.1 equivalents). The reaction was heated at 70°C with stiring for 2 hours and stirred at 25°C for 1-2 hours. Water was added, the mixture partitioned between ethyl acetate, separated, washed with brine and dried over Na_2SO_4. to give an oil (6 g). MS and H-NMR were consistent with the proposed structure.

Step B



The compound produced in Step A (6g) was dissolved in methylene chloride (50 mL). To this solution TFA (20 mL) was added. The solution was stirred for 12 hours. The solvent was removed under reduced pressure followed by addition of ether. The solid was filtered and dried in a vacuum oven for 1-2 hours.

Step C



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes, DL-ethyl 3-amino-3-pyridylpropionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography

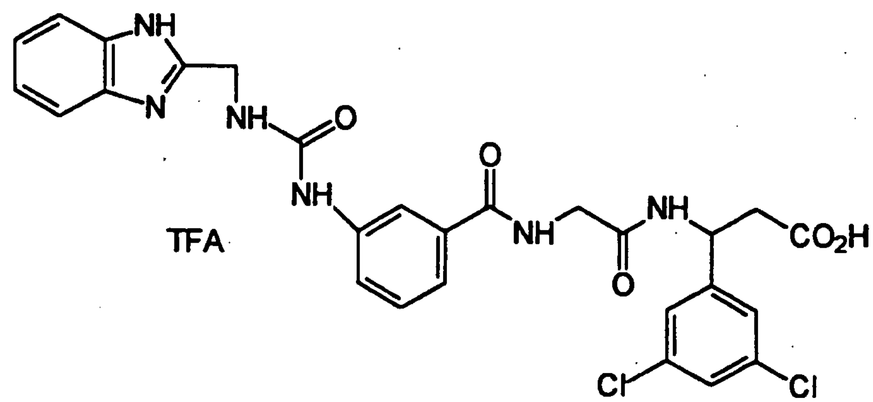
(water/acetonitrile) to result in a white solid (1.0 g). MS and H-NMR were consistent with the propos d structure.

Step D

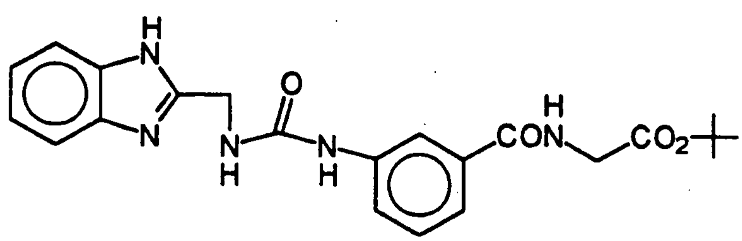
DL-ethyl 3-amino-3-pyridyl propionate adduct produced in Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 150 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 272

Preparation of β-[[2-[[[3-[[[[(1H-benzimidazol-2-yl)-methyl)amino]carbonyl]amino]phenyl]carbonyl]amino]-acetyl]amino]-3,5-dichlorobenzenepropanoic acid, trifluoroacetate salt

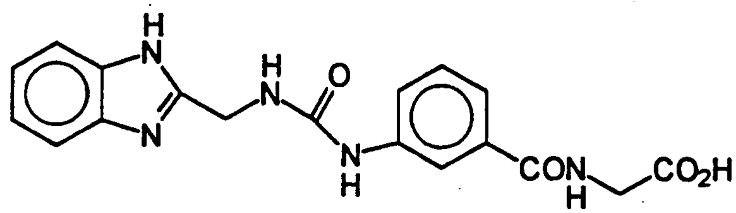


Step A



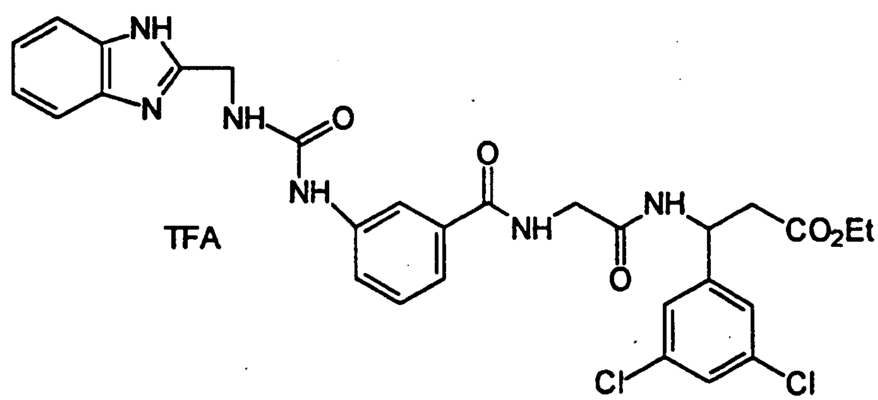
Dimethylformamide(25 mL) was added to the phenyl carbamate tert-butyl ester from Step B of Example 266, followed by addition of 2-aminomethyl benzimidazole (Aldrich) (1.1 equivalents). The reaction was heated to 70°C with stirring for 2 hours and stirred at 25°C for 1-2 hours. Water was added and the mixture partitioned between ethyl acetate, separated, washed with brine and dried over Na_2SO_4 to give an oil (6 g). MS and H-NMR was consistent with the proposed structure.

Step B



The compound produced in Step A (6 g) was dissolved in methylene chloride (50 mL). To this mixture TFA (20 mL) was added. The mixture was stirred for 1-2 hours. The solvent was removed under reduced pressure followed by addition of ether. The solid was filtered and dried in a vacuum oven for 1-2 hours.

Step C



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes, DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to r sult in a

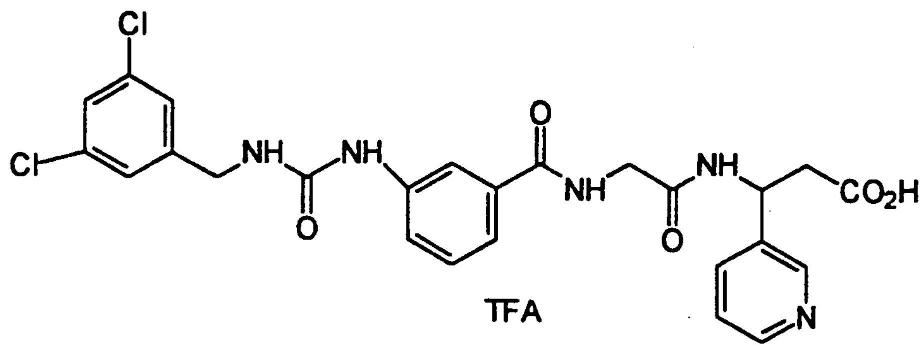
white solid (0.8 g). MS and HNMR were consistent with the proposed structur .

Step D

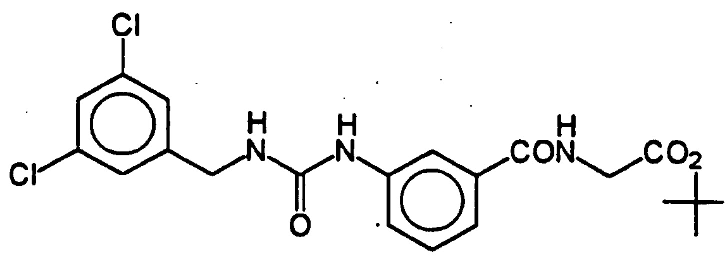
DL-ethyl 3-amino-3-(1,3-dichlorophenyl) propionate adduct produced in Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 125 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 273

Preparation of β-[[2-[[[3-[[[[(3,5-dichlorophenyl)methyl]amino]carbonyl]amino]-phenyl]carbonyl]amino]acetyl]amino]pyridine-3-propanoic acid, trifluoroacetate salt

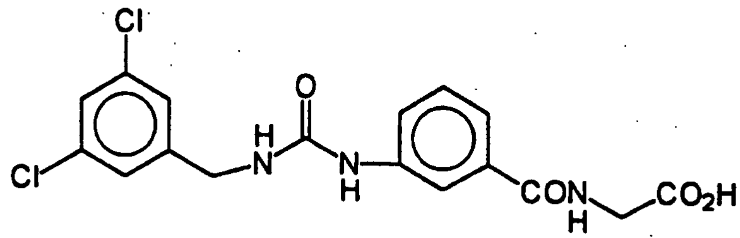


Step A



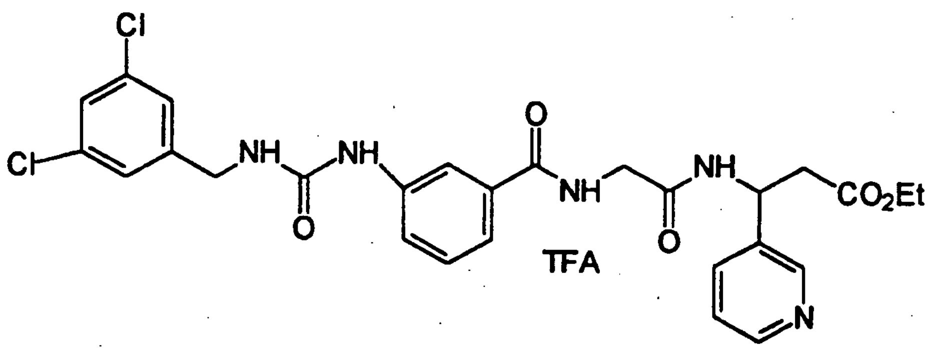
Dimethylformamide (25 mL) was added to the phenyl carbamate tert-butyl ester from Step B of Example 266, followed by addition of 3,5-dichlorobenzyl amine (Lancaster) (1.1 equivalents). The reaction was heated at 70°C with stiring for 2 hours and stirred at 25°C for 1-2 hours. Water was added and the mixture partitioned between ethyl acetate, separated, washed with brine and dried over Na_2SO_4. to give an oil (6 g). MS and H-NMR was consistent with the proposed structure.

Step B



The compound produced in Step A (6g) was dissolved in methylene chloride (50 mL). To this mixture TFA (20 mL, 4N) was added. The mixture was stirred for 1-2 hours. The solvent was removed under reduced pressure followed by addition of ether. The solid was filtered and dried in a vacuum oven for 1-2 hours.

Step C



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes, DL-ethyl 3-amino-3-(pyridyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white

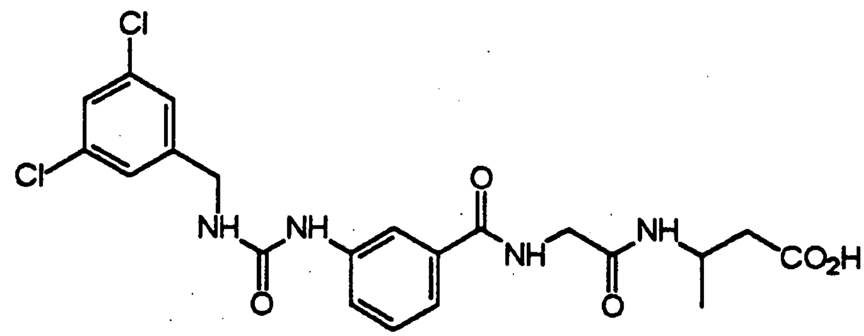
solid (0.8 g). MS and H-NMR was consistent with the proposed structure.

Step D

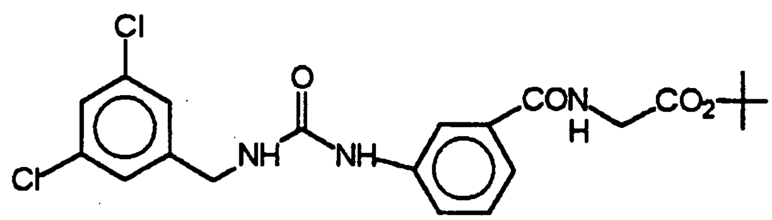
DL-ethyl 3-amino-3-(pyridyl) propionate adduct produced in Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by the addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 125 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 274

Preparation f 3-[[2-[[[3-[[[[(3,5-dichlorophenyl)-methyl]amino]carbonyl]amino]phenyl]carbonyl]-amino]acetyl]amino]butanoic acid

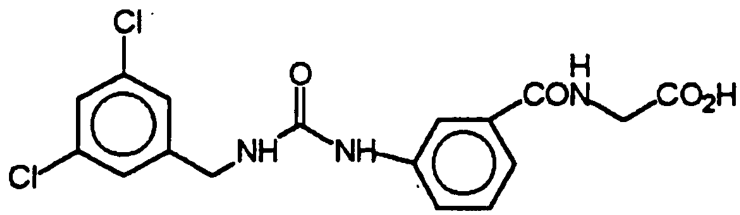


Step A



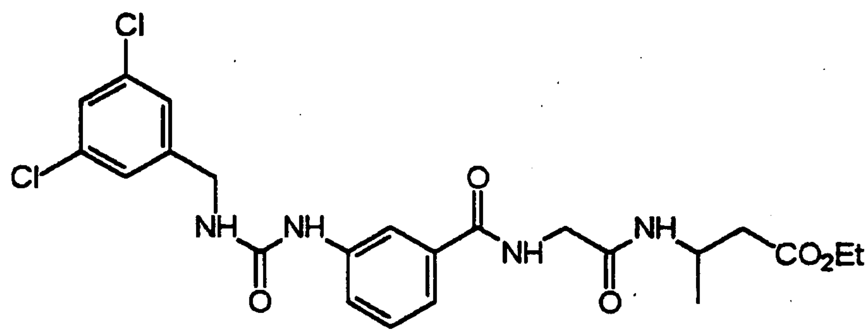
Dimethylformamide (25 mL) was added to the phenyl carbamate tert-butyl ester from Step B of Example 266, followed by addition of 3,5-dichlorobenzyl amine (Lancaster) (1.1 equivalents). The reaction was heated at 70°C with stirring for 2 hours and stirred at 25°C for 1 2 hours. Water was added and the mixture partitioned between ethyl acetate, separated, washed with brine and dried over Na_2SO_4 to give an oil (6 g). MS and H-NMR was consistent with proposed structure.

Step B



The compound produced in Step A (6 g) was dissolved in methylene chloride (50 mL). To this mixture TFA (20 mL) was added. The mixture was stirred for 1-2 hours. The solvent was removed under reduced pressure followed by addition of ether. The solid was filtered and dried in a vacuum oven for 1-2 hours. MS and H-NMR was consistent with the proposed structure.

Step C



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound produced in Step B (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL-ethyl 3-amino-3-(methyl) propionate (Aldrich) (1.1 g, 0.5 mmol) was added followed by addition of NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse phase chromatography (water/acetonitrile) to result in a white

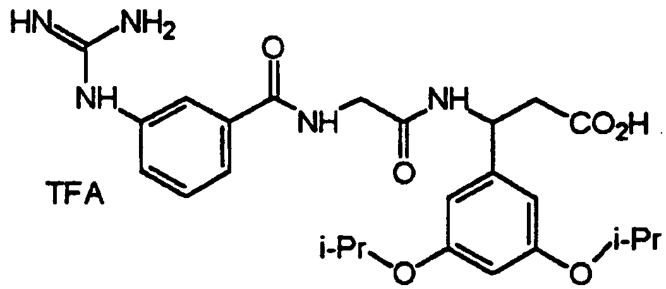
solid (0.8 g). MS and H-NMR were consistent with the proposed structure.

Step D

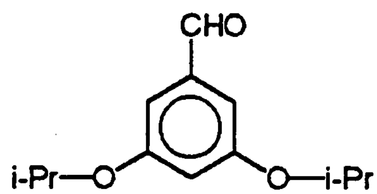
DL-ethyl 3-amino-3(methyl) propionate adduct produced in Step C (500 mg) was dissolved in water/acetonitrile (1:1), followed by addition of lithium hydroxide (100 mg). The reaction was allowed to stir at 25°C, and monitored by HPLC. After complete hydrolysis (1-2 hours) trifluoroacetic acid was added until pH = 2. The product was purified by reverse phase chromatography (water/acetonitrile) to result in 125 mg of the title compound as a white solid. MS and H-NMR were consistent with the proposed structure.

Example 275

Preparation of β-[[2-[[[3-[(aminoiminomethyl)amino]-phenyl]carbonyl]amino]acetyl]amino]-3,5-bis(1-methylethoxy)benzenepropanoic acid, trifluoroacetate salt

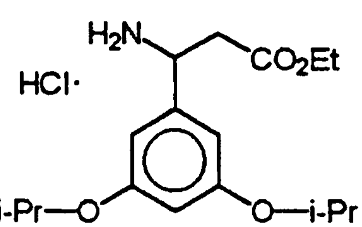


Step A



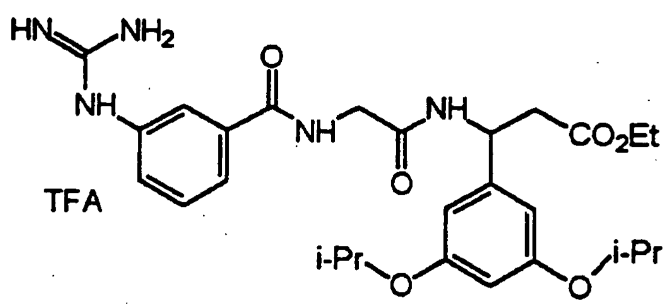
To 3,5-dihydroxybenzaldehyde (1 0.g) in acetone (100 mL) was added K_2CO_3 (20 g) and isopropyliodide (20 g). The mixture was heated at reflux and stirred for 2 days. Water (250 mL) was added and the product extracted into ethyl acetate. The organic layer was separated, washed with water, brine and dried over Na_2SO_4 to give 3,5-diisopropyloxyphenylcarboxaldehyde (12 g) as a dark oil. This material was used as is for the next step. MS and H-NMR were consistent with the proposed structure.

Step B



To 3,5-diisopropyloxyphenylcarboxaldehyde (Step A) (10.g) in ethan 1 (70 mL) was added ammonium ac tate (12.5 g) foll wed by additi n f ethyl hydrogen malonate (6.0 g). The reaction mixture was stirred at reflux for 5 hours. The mixture was cooled, and ethanol removed under reduced pressure. Aqueous HCl (100 mL) was added and the mixture partitioned with ethyl acetate. the organic layer was discarded and the acid layer made basic with solid K_2CO_3. The resulting mixture was partitioned between methylene chloride (150 mL), separated and dried over Na_2SO_4. The solvent was evaporated to give DL ethyl-3-amino-3-(3,5diisopropylphenyl) propionate as an oil. Ether (100 mL) was added, followed by addition of HCl in dioxane (20 mL, 4N) and stirred vigorously for one hour. The HCl salt was collected by filtration (4.3 g). MS and H-NMR were consistent with the proposed structure.

Step C



N,N'-disuccinimidyl carbonate (DSC) (1.0 g, 0.4 mmol) was added to the compound of Example M (1.0 g, 0.4 mmol) in dry dimethylformamide (6 mL) followed by addition of dimethylaminopyridine (100 mg). After a period of 20 minutes DL ethyl 3-amino-3-(3,5-diisopropyloxyphenyl) propionate hydrochloride (1.1 g, 0.5 mmol) was added followed by addition of NMM (2.0 mL). After complete reaction (1-16 hours) the product was purified by reverse